

Anthelmintic Activity of Pyrantel Pamoate against Hookworm, *Necator americanus*

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Since Pyrantel pamoate (1, 4, 5, 6-Tetrahydro-1-methyl-2 [(trans-2-(2 thienyl) vinyl) Pyrimidine 4, 4'-methylenebis (3-hydroxy-2-naphthoate)]) was reported to have an anthelmintic activity against nematodes (Austin *et al.*, 1966), many investigators proved that this was highly effective against a wide range of human parasitic nematodes. The present authors tested the anthelmintic activity of this drug against hookworm, *Necator americanus*. In the present paper, the result obtained is reported comparing with the efficacy of 1-bromonaphthol (2) as a control, with special reference to LPG index of the infected persons.

Materials and Methods

In order to evaluate anthelmintic efficacy of Pyrantel pamoate against hookworm, the volunteers were obtained by the stool examinations of inhabitants from 9 villages in Sata-cho, Kagoshima in July 1969 and 1970. The authors used combined method of the following examinations: thick smears, saturated NaCl floatation and polyethylene tube culture methods. The species of hookworm was determined by using the culture method. It should be taken into consideration that the efficacy of some anthelmintics would vary according to the worm burden. Based on this view, the authors estimated

the anthelmintic activity of Pyrantel pamoate (*P.p.*) in relation to LPG (number of hookworm larvae per gram feces by the culture) index of the individuals. All the persons positive for hookworm larvae by culture method were divided into 3 groups according to LPG; below 100, 101-300 and 301 or more. Those volunteers without any recognizable clinical manifestations were randomly divided again into 3 groups and each group was given orally the following dose of the drugs: Group A with Pyrantel pamoate tablet in a single dose of 10 mg base per kg of body weight; Group B, 20 mg per kg of *P.p.* tablet; and Group C, 8 g. of 1-bromonaphthol(2) (wormin) per adult, respectively. Breakfast or lunch was not given before administration. Ten to 20 g. Magnesium sulfate ($Mg SO_4$) was dissolved in water and given to the Group II 30 minutes after the administration of anthelmintics. The worms were collected from their stools discharged during 24 hour period. Other persons who were administered only with anthelmintics were included in Group I. Side effects complained within 24 hours after the administration were recorded. Approximately 3 weeks after the drug administration, post-treatment fecal examinations were performed.

Results

A preliminary survey revealed that 640 (29.5%) out of 2,172 persons from 9 villages examined were positive for hookworm eggs. The positive rate of the individual villages fluctuated ranging from 8.9% to 42.9%.

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All the infective larvae obtained by culture method were identified as those of *Necator americanus* and the 95% of carriers was found being light infection, that is, LPG: <1,000.

The result of post-treatment examination was shown in Table 1. In Group II, the cure rates observed in A, B and C groups were 77.6% (38/49), 86.5% (45/52) and 86.8% (46/53), respectively. No statistically significant difference among cure rates was seen. In Group I, the cure rates in A, B and C groups were 71.4% (50/70), 84.6% (66/78) and 91.4% (64/70), respectively. Although no significant difference existed between Groups B and C, there was a highly significant difference between Group A and Group C ($p < 0.01$, $\chi^2 = 9.26$). No significant difference

was seen between the groups with or without laxative.

Relation between the cure rates under different doses of *P.p.* and LPG index was shown in Table 2. In Group A, the cure rates were 92.3% (48/52), 82.1% (23/28) and 46.2% (12/26) in those whose LPG were below 100, 101-300 and 301 or more, respectively. In those whose LPG was 301 or more, the cure rate was significantly lower than that in group whose LPG was 101-300 ($p < 0.01$, $\chi^2 = 7.65$). While in Group B, the cure rates of 90.6% (48/53), 92.3% (24/26) and 59.4% (16/27) were obtained in those whose LPG were below 100, 101-300 and 301 or more, respectively. There was also similar tendency in the cure rates which were inversely proportional to LPG. There

Table 1 Anthelmintic efficacies of Pyrantel pamoate and 1-bromonaphthol (2) against *Necator americanus*

	Pyrantel pamoate		1-bromonaphthol(2)***			
	10 mg/kg (A)		20 mg/kg (B)		(C)	
	No. of cases	No. of cases cured (%)	No. of cases	No. of cases cured (%)	No. of cases	No. of cases cured (%)
Group I *	70	50(71.4)	78	66(84.6)	70	64(91.4)
Group II **	49	38(77.6)	52	45(86.5)	53	46(86.8)

* Group I: Administered only with anthelmintics.

** Group II: Administered with a laxative, MgSO₄, 30 minutes after the administration of anthelmintics.

*** Adult dose, 8 g. per person.

Table 2 Anthelmintic efficacies of Pyrantel pamoate and 1-bromonaphthol (2) against *Necator americanus* in relation to LPG index

Anthelmintics	LPG	Cure rate					
		No. of cases	below 100 No. of cases cured (%)	No. of cases	101-300 No. of cases cured (%)	No. of cases	301 or more No. of cases cured (%)
(A) Pyrantel pamoate	10 mg/kg	52	48(92.3)	28	23(82.1) ^a	26	12(46.2) ^b
(B) Pyrantel pamoate	20 mg/kg	53	48(90.6)	26	24(92.3) ^c	27	16(59.4) ^d
(C) 1-bromonaphthol (2)	8 g.	50	46(92.0)	28	25(89.3)	32	27(84.4) ^e

* Statistical differences between: a and b: $P < 0.01$, $\chi^2 = 7.65$; c and d: $P < 0.05$, $\chi^2 = 6.13$; b and e: $P < 0.01$, $\chi^2 = 9.51$; d and e: $P < 0.05$, $\chi^2 = 4.67$

was a significantly low cure rate in the carriers whose LPG was 301 or more, as compared with those whose LPG, 101-300 ($p < 0.05$, $\chi^2 = 6.13$). On the other hand, in Group C, cure rates of 92.0% (46/50), 89.3% (25/28) and 84.4% (27/32) were obtained corresponding to LPG indices, below 100, 101-300 and 301 or more, respectively. No statistically significant difference was seen among these rates.

Table 3 shows the result of adult worm collections from stools by administering laxative in addition to the anthelmintics. Adult worms, 107 worms (91 females and 16 males) in total, were found to have been expelled from 22 (31.0%) persons out of 71 persons examined in Group A. The average number of female worms was 1.3 per person examined. While in Group B, 43.5% (30/69) was found to have expelled worms. A total of 172 (123 females and 49 males) adult specimens were obtained. The average number of female worms was 1.8 per person examined. Furthermore, 31 cases (43.1%) out of 72 persons were found to have discharged worms in Group C. A total of 258 (209

females and 49 males) worms were recovered in this group. The average number of female per person examined was 2.9. The relationships between LPG index and the number of adult worms expelled, were shown in Table 4. The average number of female worms per person examined was 1.1, 2.6 and 5.2 in groups whose LPG were below 100, 101-300 and 301 or more, respectively.

The side reactions occurring within 24 hours after the administration of anthelmintics were summarized in Tables 5 and 6. Table 5 shows the side reactions shown in persons administered only anthelmintics. In Groups A and B, 12.5% (3/24) and 15.2% (5/24), respectively, were with various complaints. While, 63.8% (44/69) of the cases from Group C were with complaints. As compared with 1-bromonaphthol (2), the administration of Pyrantel pamoate yielded less side reactions. Main complaints caused by *P.p.* were dizziness, abdominal pain, headache, stomachache, vomiting, nausea and diarrhea. Most of these symptoms were observed to occur within 4 hours after the administration. The side reactions shown

Table 3 Number of adult *Necator americanus* expelled by anthelmintics.

Anthelmintics	No. of cases	No. of cases who expelled worms(%)	Total no. of worms found (males and females, each)	Average no. of female worms per person administered with anthelmintics
(A) Pyrantel pamoate 10 mg/kg	71	22(31.0)	107(16, 91)	1.3
(B) Pyrantel pamoate 20 mg/kg	69	30(43.5)	172(49,123)	1.8
(C) 1-bromonaphthol (2) 8 g.	72	31(43.1)	258(49,209)	2.9
Total	212	83(39.2)	537(114,423)	2.0

Table 4 Relationship between LPG index and the number of adult worms expelled by anthelmintics and laxative

LPG	No. of cases treated	No. of cases who expelled worms (%)	Total no. of worms found (males and females each)	Average no. of female worms per person administered with anthelmintics
below 100	76	29(38.2)	108(23, 85)	1.1
101-300	50	28(56.0)	153(23,130)	2.6
301 or more	40	24(60.0)	267(65,208)	5.2

Table 5 Side reactions shown in persons within 24 hour after the administration of Pyrantel pamoate and 1-bromonaphthol (2)

Anthelmintics	Pyrantel pamoate				1-bromonaphthol (2)	
	10 mg/kg (A)		20 mg/kg (B)		8 g. (C)	
	within 4 hrs	4-24 hrs	within 4 hrs	4-24 hrs	within 4 hrs	4-24 hrs
Dizziness	1		2		7	
Abdominal pain		1	1		15	3
Headache	2	1		1	25	4
Stomachache	1		1		5	2
Nausea	1				1	
Vomiting					17	4
Fever				1	4	1
Anorexia					5	1
Fatigue					2	
Constipation					4	3
Rash					1	
Diarrhea		3	3	3	27	23
The ratio: No. of persons with complaints to No. of examined (%)	3/24(12.5)		5/33(15.2)		44/69(63.8)	

* Diarrhea was omitted from calculations.

by the additional administration of Magnesium sulfate after anthelmintics are shown in Table 6. In Groups A and B, 36.1% (22/61) and 38.6% (22/57) of persons, respectively, complained miscellaneous symptoms mentioned above. However, in Group C, the persons with side reactions were 60.4% (67/111). These results indicate that the additional administrations of Magnesium sulfate resulted much more complaints in comparison with the administration of *P.p.* alone. It can be noted that *P.p.* itself is one of the recommendable drugs as an anthelmintic because of its less side effects.

Discussions

The anthelmintic efficacy of *P.p.* against *N. americanus* has been already reported by several investigators. Desowitz *et al.* (1970) showed that by a daily dose of pyrantel suspension 5 mg/pound of body weight for 3 consecutive days, 83.7% (36/56) of the sub-

jects were completely cured. Yokogawa *et al.* (1970) and Tsuji *et al.* (1971) also exhibited *P.p.* to be highly effective by a single administration of 10 or 20 mg/kg. According to these authors, the cure rates were 76.4% (13/17) by 10 mg/kg, 78.5% (11/14) by 20 mg/kg (Yokogawa *et al.*), 75.0% (6/8) by 10 mg/kg and 90.0% (9/10) by 20 mg/kg (Tsuji *et al.*), respectively. On the other hand, Kobayashi *et al.* (1971) found that only 45.5% (10/22) by 10 mg/kg and 52.25% (12/23) by 20 mg/kg were cured. Ishizaki *et al.* (1971) also reported that the cure rates were 69% (22/32) by a single dose of 10 mg/kg and 89% (25/28) by the same dose of Pyrantel for 3 consecutive days.

In our study, as shown in Table 1, *P.p.* was highly effective against *N. americanus* infections. This will agree with the results by Yokogawa *et al.* (1970) and Tsuji *et al.* (1971). Further, in our study, the cure rate obtained by 20 mg/kg *P.p.* was considerably higher than that by 10 mg/kg. However,

Table 6 Side reactions shown in persons within 24-hour after the administration of MgSO₄ in addition to either Pyrantel pamoate or 1-bromonaphthol (2)

Anthelmintics	Pyrantel pamoate				1-bromonaphthol (2)	
	10 mg/kg (A)		20 mg/kg (B)		8 g. (C)	
	within 4 hrs	4-24 hrs	within 4 hrs	4-24 hrs	within 4 hrs	4-24 hrs
Dizziness	1	1	1		13	7
Abdominal pain	7		7	6	18	6
Headache	5	1	4	1	20	7
Stomachache	1			2	7	4
Nausea	21	1	2		1	1
Vomiting	4		5	1	16	6
Fever	1					1
Anorexia	2	2	2	2	6	7
Fatigue	2	2		2	1	
Constipation		2	2		2	3
Diarrhea	26	37	23	38	51	54
The ratio : No. of persons with complaints to No. of examined (%)	22/61 (36.1)		22/57 (38.6)		67/111 (60.0)	

* Diarrhea was omitted from calculations

there was an obvious difference between the cure rates reported by Kobayashi *et al.* (1971) and cure rates of others including us even when using the same dose of *P.p.*.

Komiya and Sato (1954) pointed out that the "over-estimation tendency" in cure rate was caused by the methods adopted at pre- and post-treatment examinations and the high percentage of cure rates was often seen in the case of light infection. From the latter point of view, the present authors induced LPG index as an indicator of worm burden and found that most volunteers (95 %) were with light infection (LPG : <1,000). The volunteers used by some of previous investigators are also considered with light infection judging from several indices [LPG : <1,000, No. of expelled female worms/person : 2.1 by Yokogawa *et al.* (1970) ; No. of expelled female worms/person : 1.6 by Tsuji *et al.* (1971) and average EPG : 374 (a single dose of 10 mg *P.p.*/kg), 813 (a daily dose of 10 mg *P.p.*/kg for 3 consecutive days) by Ishizaki *et al.* (1971)]. Although Kobayashi

et al. (1971) did not report as to this point, these data suggest that the difference in cure rates reported by investigators mentioned above was caused partly by the reason pointed out by Komiya and Sato (1954).

Furthermore, it is noticeable that the present authors observed a considerable reduction in cure rate in the group whose LPG was 301 or more, although this group was also considered with light infection. This reveals the importance of informations about worm burden of volunteers when the efficacy of some anthelmintics are to be evaluated.

Summary

Pyrantel pamoate was tested for its anthelmintic efficacy against hookworm, *N. americanus* infection comparing with 1-bromonaphthol (2). Volunteers were divided into 3 groups based on their LPG (number of larvae per 1 gram of stool by culture method) and each group was divided further into 3

groups: A, B and C according to the dose and drug administered. Group A was given orally a single dose of 10 mg/kg *P.p.* tablet, Group B, 20 mg/kg *P.p.* tablet and Group C, 8 g. (adult dose) of 1-bromonaphthol (2).

Post-treatment fecal examinations were carried out 3 weeks later. In Group A the cure rates obtained were 92.3 % (48/52), 82.1 % (23/28) and 46.2 (12/16) in the subjects whose LPG were below 100, 101-300 and 301 or more, respectively. A highly significant difference in cure rates was seen between LPG 101-300 and LPG 301 or more. In Group B cure rates were 90.6 % (48/53, LPG : below 100); 92.3 % (24/26, LPG : 101-300); and 59.4 % (16/27, LPG : 301 or more), respectively. There was a considerable reduction in cure rate in the subjects whose LPG was 301 or more.

On the other hand, in Group C cure rates obtained were 92.0 % (46/50), 89.3 % (25/28) and 84.4 % (27/32) in the carriers whose LPG were below 100, 101-300 and 301 or more, respectively. It was observed that in the carriers whose LPG was 301 or more, the cure rate obtained by *P.p.* in Groups A and B were significantly lower than that of 1-bromonaphthol (2) in Group C.

It was clarified that *P.p.* caused less side reactions in comparison with 1-bromonaphthol (2).

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**Pyrantel pamoate のアメリカ鉤虫 (*Necator americanus*)
に対する駆虫効果**

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Pyrantel pamoate 錠 (以下 *P.p.*) および 1-bromonaphthol (2) 顆粒 (Wormin) を用いて *Necator americanus* (以下 *N.a.*) に対する駆虫効果を検討し、次の成績を得た。

1. 鹿児島県佐多町の住民 2,172 名についての検査で鉤虫卵陽性者 640 名 (29.5%) を得たが、培養法ならびに一部の駆出虫体による検査の結果は全て *N.a.* の単独感染者で、その 95% は LPG 1,000 以下であった。

2. 投薬は *P.p.* 10 mg/kg, 20 mg/kg および Wormin (大人量 8 g.) を用いたがその陰転率は、Table 1 の如く *P.p.* と Wormin 投与群における駆虫効果には差がな

かった。

3. 感染者を LPG 100 以下, 101~300, 301 以上の 3 群に分けて駆虫効果を検討するに、Wormin 投与群では夫々 92.0%, 89.3%, 84.4% の陰転率を示した。一方、*P.p.* 投与群では 10 mg/kg の場合、夫々 92.3%, 82.1%, 46.2% であり、20 mg/kg の場合夫々 90.6%, 92.3%, 59.4% の陰転率を示した。即ち、LPG 301 以上の群において著しい陰転率の低下が認められた (Table 2)。このことは駆虫効果の判定を行なう際に投薬対象者の感染量に注目すべき事を示唆している。

4. 副作用については *P.p.* 投与群の場合発現率は 15.2~38.6% で Wormin 投与群での発現率 60~63.8% に比較して軽度であった (Table 4, 5)。

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