

CLINICAL TRIALS WITH PYRANTEL PAMOATE IN INTESTINAL PARASITOSEs

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S U M M A R Y

There have been treated, with pyrantel pamoate, per os, 127 patients with various intestinal parasitoses, the doses used being 10 mg/kg/day X 1, 10 mg/kg/day X 3, 20 mg/kg/day X 2 and 20 mg/kg/day X 3. Parasitological control was performed by using Kato's and Stoll's quantitative methods as well as Graham's (Scotch tape) and Bearmann's methods. Ancylostomidae and *Trichuris* worms were recovered by skimming 24-hour feces, on four successive days. The percentages of cure obtained with the schedule 10 mg/kg/day X 1 were 100.0% and 84.6% for ascariasis and enterobiasis, respectively. As regards ancylostomiasis, the total doses of 30, 40 and 60 mg/kg produced, respectively, the following percentages of cure — 57.1, 75.0 and 88.8%. At these dosages, the drug demonstrated partial activity against *Trichuris*. When complete cure was not achieved, a marked decrease in the mean number of hookworm and whipworm eggs was observed. A group of 11 patients treated with 20 mg/kg/day X 2 presented 75.0% of cure in ancylostomiasis and 42.8% in trichuriasis. Thirty days later, the same schedule of treatment was repeated. Parasitological control, however, did not reveal further decrease in the mean number of whipworm eggs, just one patient having been cured. Nevertheless, the 3 patients with hookworm infection presented negative tests. As concerns *Strongyloides stercoralis*, no therapeutic action could be observed. Tolerance to the drug has proved satisfactory, just 5 patients having presented diarrhea, and two others, vomiting, on the day following the first dose. Due to the low occurrence of side effects and to its high efficacy, pyrantel pamoate, a polyvalent antihelminthic, should be tried in mass treatment of intestinal parasitoses.

I N T R O D U C T I O N

Pyrantel tartrate was obtained, in 1966, by AUSTIN et al.³, who demonstrated its high efficacy against various intestinal parasites in domestic animals.

Pyrantel pamoate (Fig. 1), consisting of pyrantel (trans-1-methyl-2(2-thienyl) vinyl) 1, 4, 5, 6, tetrahydropyrimidine) plus pamoate acid, is an insoluble salt, scarcely absorbed by the intestine and displaying marked antiparasitical action.

Clinical trials carried out by BUMBALO et al.⁴, DESOWITZ et al.⁵, AMATO NETO et al.², YOKOGAWA et al.¹¹, LEVI et al.⁷ and RODRIGUES & MARTIRANI¹⁰, among others, demonstrated this compound to be active in ascariasis, enterobiasis and ancylostomiasis.

Some question still remains as to its range of action in *Trichuris trichiura* and *Strongyloides stercoralis*, as well as to the best

This work has been supported by the Conselho Nacional de Pesquisas, Brazil

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schedule of treatment to be used against other parasites aforementioned.

The present paper presents the data obtained with pyrantel pamoate in clinical trials against the most prevalent helminthiasis in our country.

and/or *Trichuris* infection besides being parasitized on a smaller scale, with other helminths — were daily given 20 mg/kg (divided into two doses) for 2 days. The patients (11) showing not to be cured of their ancylostomidae and/or *Trichuris* infection

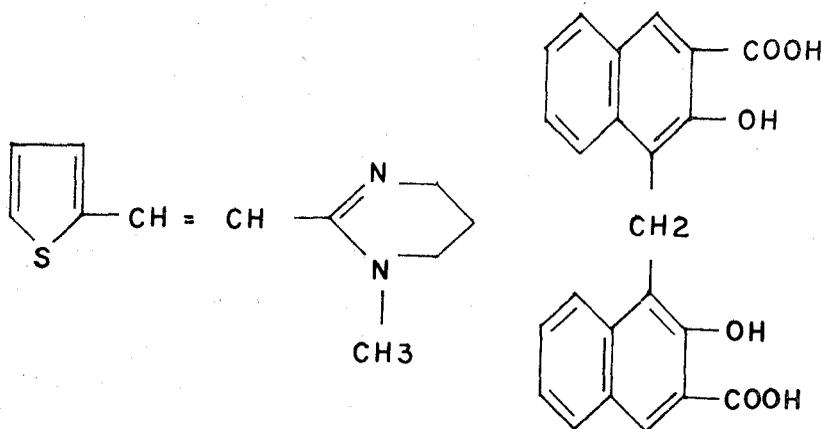


Fig. 1 — Chemical structure of pyrantel pamoate

MATERIAL AND METHODS

There have been treated 127 patients (male and female), 116 of them being children (aged 5 to 15 years) and the remaining 11, adults (aged 16 to 31 years). The former patients lived at an orphanage (Missão Ramacrisna, Vianópolis, MG) and the latter ones, at Instituto Bom Pastor (Belo Horizonte, MG).

Therapeutic Schedules

Group A — 47 children, parasitized with *Ascaris lumbricoides*, *Trichuris trichuria* and *Enterobius vermicularis*, were treated, per os, with a single 10 mg — dose of pyrantel pamoate per kg of body weight.

Group B — 50 children, infected with the 3 aforementioned parasites, as well as with ancylostomidae and *Strongyloides stercoralis*, were administered 10 mg of the drug per kg of body weight, for 3 consecutive days.

Group C — 20 patients, from 12 to 31 years of age, presenting mild ancylostomidae

resumed this same therapeutic schedule 30 days after the end of the first treatment.

Group D — 10 children, selected in the same way as those picked out for Group C, received, for 3 consecutive days, 20 mg/kg divided into 2 doses.

Group E — Control group, comprising 47 multi-parasitized patients (aged 5 to 15 years) who were not submitted to any treatment.

In the beginning, Groups A and B comprised 2 subgroups, one of which received the compound in suspension (50 mg/ml) and, the other, in tablets (125 mg). Considering the similarity of results obtained with the two formulations, those 2 subgroups were taken into consideration as a single whole. Groups C and D received just tablets.

To Groups A and B, the drug was administered only in the morning, after breakfast, but Groups C and D were also given the compound in the afternoon. All patients under treatment showed good clinical condition.

Parasitological Control — Assessment of drug therapy was performed through the quantitative copro-parasitological methods of KATO and STOLL and the qualitative methods of Bearmann (modified by MORAES) and of Graham (Scotch tape). The slides prepared for Kato's method contained about 40 mg of feces and those used for Stoll's, 0.075 ml (which is equivalent to 5 mg of feces).

Before treatment, two parasitological tests were performed, and, after treatment, tests were carried out on the 14th, 16th, 28th and 30th days. The mean number of eggs presented on all Tables refer to the data from two successive stool examinations. After treatment, patients presenting negative stool examinations (after Kato's, Stoll's, Bearmann's and Graham's methods) were considered cured.

For better therapeutic control of Groups C and D, there was also performed the recovery of worms, from 24-hour feces, on the first four days before and after treatment, the technique used being the one described by MAGALHÃES and, later on, modified by us. Such technique requires a metal-sheet cylinder (14.0 cm in diameter and 18.5 cm in height) to which a wire net is adapted, at each end, the upper net having 0.9 mm meshes and, the lower one, 0.5 mm.

The procedure is as follows: 24-hour feces are fixed and emulsified in 5% formalin for 60 minutes and, afterwards, placed upon the wire net at the top of the cylinder. Skimming is then performed under pressure of water from a shower previously adapted to the tap,

the sediment remaining on the wire net being removed to a Petri dish under pressure of water. The worms recovered are then clarified by Amann's lacto-phenol solution and classified under microscope.

RESULTS

Group A

Table I shows the percentages of cure for ascaridiasis, trichuriasis and enterobiasis, to have been, respectively, 94.2, 32.2 and 100.0, in accordance with the tests performed 14 days after treatment, while, according to those carried out 28 days after the end of treatment, such percentages were shown to be 100.0, 17.8 and 84.6, respectively. It must be pointed out that the 5 patients whose stool examinations remained positive for *Enterobius* were, all of them, infected with the 3 parasites referred to above, cure having been achieved only for their ascaridiasis.

It is worth remarking that if the Scotch tape method had been used, after treatment for seven consecutive days, instead of only two, percentage of patients not cured would probably have increased.

The decrease in the mean number of ascaris eggs per patient was about 98%, as demonstrated by both Kato's and Stoll's methods (Table II).

Concerning trichuriasis, such decrease (14 and 28 days after the end of treatment) was seen to be 38.5%, by Kato's method and, by Stoll's, 64.5% and 71.6% (Table II).

TABLE I

Data from 47 children treated with a single 10 mg/kg dose of pyrantel pamoate (Group A)

Helminth	Patients treated	Patients Cured — After	
		14-16 days	28-30 days*
<i>Ascaris</i>	35	33 (94.2)	35 (100.0)
<i>Trichuris</i>	31	10 (32.2)	5 (17.8)
<i>Enterobius</i>	27	27 (100.0)	22 (84.6)

() : Percentage of cure

* : The 28-30 days control was performed on 44 patients

Group B

100.0 for enterobiasis and 36.3 and 30.3 for strongyloidosis.

Table III shows the percentages of cure (14 and 28 days after treatment) to have been 95.0 for ascariasis, 5.2 and 15.7 for trichuriasis, 71.4 and 57.1 for ancylostomiasis,

There has been observed a marked decrease in the total number of eggs eliminated by the patients infected with *Ascaris lumbricoides*. Indeed, by Kato's method, 293,725

TABLE II

Fluctuation in the total and mean number of eggs from the feces of 47 children treated with a single 10 mg/kg dose of pyrantel pamoate (Group A)

Helminth		<i>Ascaris</i>			<i>Trichuris</i>			
		Before	After		Before	After		
			14-16 days	28-30 days		14-16 days	28-30 days	
Copro-parasitological Examinations	Kato	Total no. of eggs/g	232,484	174	0	13,529	6,678	7,216
		no. of patients	32	2	0	30	24	26
	Stoll	Mean no. of eggs/g/patient	7,265	87 (98.8)	0 (100.0)	450	278 (38.5)	277 (38.5)
		Total no. of eggs/g	182,800	200	0	11,300	5,200	4,900
	Stoll	no. of patients	29	1	0	10	13	15
		Mean no. of eggs/g/patient	6,303	200 (96.8)	0 (100.0)	1,130	400 (64.5)	326 (71.6)

() : Percentage of reduction

TABLE III

Data from 50 children treated with pyrantel pamoate at the dosage of 10 mg/kg/day X 3 (Group B)

Helminth	Patients treated	Patients Cured — After	
		14-16 days	28-30 days
<i>Ascaris</i>	40	38 (95.0)	38 (95.0)
<i>Trichuris</i>	38	2 (5.2)	6 (15.7)
<i>Ancylostomidae</i>	35	25 (71.4)	20 (57.1)
<i>Enterobius</i>	35	35 (100.0)	35 (100.0)
<i>Strongyloides</i>	33	12 (36.3)	10 (30.3)

() : Percentage of cure

TABLE IV

Fluctuation in the total and mean number of eggs from the feces of 50 children treated with pyrantel pamoate at the dosage of 10 mg/kg/day X 3 (Group B)

Helminth		<i>Ascaris</i>			<i>Trichuris</i>			Ancylostomidae			
Treatment		Before	After		Before	After		Before	After		
			14-16 days	28-30 days		14-16 days	28-30 days		14-16 days	28-30 days	
Copro-parasitological Examinations	Kato	Total no. of eggs/g	293,725	2,762	19,254	22,575	17,984	22,252	2,258	138*	2,146
		no. of patients	38	2	2	38	35	30	25	2*	16
		Mean no. of eggs/g/ patient	6,528	1,381 (78.9)	9,627 (0.0)	594	513 (13.7)	741 (0.0)	90	69 (23.4) *	134 (0.0)
	Stoll	Total no. of eggs/g	248,100	1,900	7,600	17,400	11,100	14,600	9,800	2,300	2,600
		no. of patients	38	2	1	16	23	21	27	10	16
		Mean no. of eggs/g/ patient	7,729	950 (87.8)	7,600 (1.7)	1,087	482 (55.7)	695 (35.7)	362	230 (37.0)	260(28.2)

() : Percentage of reduction

* : Examination performed on 15 patients

eggs per gram of feces, before treatment, were seen to come down to 19,254 after treatment and, by Stoll's method, from 248,100 to 7,600.

The elimination of hookworm and *Trichuris* eggs, however, was not significantly affected by treatment, their total number having remained practically the same, as shown when Kato's method was used for the assessment for results (Table IV).

Group C

Regarding the 20 patients treated with 20 mg/kg/day X 2, the percentages of cure obtained were 42.8, for trichuriasis, and 75.0 for ancylostomiasis.

The total number of worms eliminated in the 4 days following the end of treatment was 12 for *Trichuris* and 65 for ancylostomidae.

TABLE V

Data from 20 patients treated with pyrantel pamoate at the dosage of 20 mg/kg/day X 2, only the results from Stoll's method having been considered (Group C)

Helminth	Patients treated	Total no. of eggs		no. of patients		Total no. of worms recovered
		Treatment		Cured	Who eliminated worms	
		Before	After			
<i>Trichuris</i>	13	13,230	8,900	6 (46.1)	7 (53.8)	10
Ancylostomidae	11	24,500	200	9 (81.8)	9 (81.8)	56

() : Percentage
After: 28-30 days

TABLE VI

Fluctuation in the total and mean number of eggs from 20 patients treated with pyrantel pamoate at the dosage of 20 mg/kg/day X 2 (Group C)

Helminth		<i>Ascaris</i>			<i>Trichuris</i>			
		Before	After		Before	After		
			14-16 days	28-30 days		14-16 days	28-30 days	
Copro-parasitological Examinations	Kato	Total no. of eggs/g	15,032	5,875	7,408	8,910	204	98
		no. of patients	14	9	8	11	3	2
		Mean no. of eggs/g/patient	1,073	652 (39.2)	926 (13.7)	810	68 (91.6)	49 (93.5)
	Stoll	Total no. of eggs/g	13,230	2,400	8,900	24,500	700	200
		no. of patients	13	6	7	10	2	2
		Mean no. of eggs/g/patient	1,017	400 (60.7)	1,271 (0.0)	2,450	350 (85.8)	100 (96.5)

() ; Percentage of reduction

When cure was not achieved, there was observed a decrease of about 95.0% in the mean number of eggs per gram of feces of ancylostomidae patients, whereas, with regard to trichuris patients, no decrease could be detected (Table V and VI).

After the end of the 2nd course of treatment (performed under the same therapeutic schedule) to which were submitted 11 pa-

tients infected with *Trichuris trichiura* and 3, with ancylostomidae, no decrease in the number of *Trichuris* eggs per individual was observed. However, 4 patients (3 ones infected with ancylostomidae, and 1, with *Trichuris trichiura*) were seen to get cured.

After this 2nd treatment, only 1 *Trichuris trichiura* and 1 *Necator americanus* could be recovered from the feces.

TABLE VII

Data from 10 patients treated with pyrantel pamoate at the dosage of 20 mg/kg/day X 3, only the results from Stoll's method having been considered (Group D)

Helminth	Patients treated	Total no. of eggs		no. of patients		Total no. of worms recovered
		Treatment		Cured	Who eliminated worms	
		Before	After			
<i>Trichuris</i>	7	7,100	2,300	3 (42.9)	6 (83.8)	27
Ancylostomidae	10	18,300	100*	8* (88.8)	8* (88.8)	65

() : Percentage

* : Control (28-30 days) performed on 9 patients

TABLE VIII

Fluctuation in the number of eggs from the feces of 10 children treated with pyrantel pamoate at the dosage of 20 mg/kg/day X 3 (Group D)

Helminth		<i>Trichuris</i>			Ancylostomidae			
		Before	After		Before	After		
			14-16 days	28-30 days		14-16 days	28-30 days	
Copro-parasitological Examinations	Kato	Total no. of eggs/g	11,230	3,248	4,510	21,981	74	0
		no. of patients	9	3	7	10	3	0
		Mean no. of eggs/g/patient	1,247	428 (65.7)	643 (48.5)	2,198	25 (98.9)	0 (100.0)
	Stoll	Total no. of eggs/g	7,100	1,300	2,300	18,300	0	100
		no. of patients	7	2	4	10	0	1
		Mean no. of eggs/g/patient	1,014	650 (35.9)	560 (44.8)	1,830	0 (100.0)	100 (94.6)

() : Percentage of reduction

Group D

As shown on Table VII and VIII, the percentages of cure for ancylostomiasis and trichuriasis were, respectively, 88.8 and 22.2, and the decrease in the mean number of eggs per patient, around 97% and 45%, the results of both coproparasitological methods being taken into account.

TABLE IX

Control Group: Data from 47 untreated children (Group E)

Helminth	no. of patients	"Cure" after 28-30 days
<i>Ascaris</i>	30	3 (10.0)
<i>Trichuris</i>	33	5 (15.1)
Ancylostomidae	37	13 (35.1)
<i>Enterobius</i>	26	8 (30.7)
<i>Strongyloides</i>	14	5 (35.7)

() : Percentage of cure

From the patients in this group, 27 *Trichuris trichiura* and 85 ancylostomidae worms were recovered.

It is worth observing that, before treatment, no worms could be recovered from 24-hour feces of patients in Groups C and D.

Group E

This group, serving as control, presented the following percentages of cure (Table IX):

ascariasis	—	10.0%
trichuriasis	—	15.1%
ancylostomiasis	—	35.1%
enterobiasis	—	30.7%
strongyloidosis	—	35.7%

As can be seen from Table X, Kato's method revealed 35 patients positive for ancylostomidae, whereas Stoll's showed just 19. Likewise, Kato's method uncovered a larger number of *Trichuris* patients.

Although all parasitoses referred to above having presented some percentage of negative stool examinations ("cure"), no decrease in the mean number of eggs per patient could be observed.

TABLE X

Fluctuation in the number of eggs recovered from the feces of 47 untreated children. Examinations performed with 28-30 days intervals

Helminth		<i>Ascaris</i>		<i>Trichuris</i>		Ancylostomidae		
		1st exam	2nd exam	1st exam	2nd exam	1st exam	2nd exam	
Copro-parasitological Examinations	Kato	Total no. of eggs/g	279,423	283,578	24,589	32,431	5,756	8,798
		no. of patients	27	28	33	32	35	22
		Mean no. of eggs/g/patient	10,326	10,127 (2.0)	745	10,130 (0.0)	164	399 (0.0)
	Stoll	Total no. of eggs/g	194,950	207,200	15,500	18,400	10,900	15,700
		no. of patients	26	30	23	15	19	19
		Mean no. of eggs/g/patient	7,549	6,907 (8.6)	673	1,226 (0.0)	572	826 (0.0)

() : Percentage of reduction

It ought to be emphasized that Kato's method revealed, in every case, a larger number of patients eliminating eggs in their feces, especially regarding those individuals whose number of eggs per gram was lowest then 200.

Side Effects — Only 5 patients presented diarrhea and, two others, vomiting, on the first day after the beginning of treatment. Such symptoms, however, proved to be mild and transitory having occurred with just 2 therapeutic schedules: 10 mg/kg/day X 3 and 20 mg/kg/day X 3.

DISCUSSION

The results so far obtained with pyrantel pamoate show this drug to be highly effective against ascariasis and enterobiasis in a single dose of 10 mg per kg of body weight.

It is worth mentioning that, when assessing drug therapy, it is necessary to take into consideration not only the decrease in the mean number of eggs per gram of feces and per patient, but also the reduction in the total number of eggs per gram. As has been observed with regard to Group B, the mean number of eggs/gram/patient not cured remained about the same after treatment, in spite of the percentage of cure in the group having been 95.0%.

As regards ascariasis, pyrantel pamoate has displayed marked therapeutic action (about 80%), in doses of 20 mg/kg/day X 2 and of 20 mg/kg/day X 3, when administered to patients presenting mild infection.

DESOWITZ et al.⁵ and YOKOGAWA et al.¹¹, although using still smaller doses, have reported percentages of cure similar to those recorded in the present paper. According to the data obtained by YOKOGAWA et al.¹¹, *Ancylostoma duodenale* has proved more susceptible to pyrantel pamoate than *Necator americanus*.

It must be emphasized that, in Brazil, the latter parasite is predominant. In the present study, the percentages of *Necator* and *Ancylostoma* eliminated were found to be 90.4 and 9.6, respectively.

In therapeutic schedules using larger doses of pyrantel pamoate, there could be detected

partial activity of the drug against trichuriasis, as demonstrated by the decrease in the mean number of eggs/gram/patient and by the worms recovered from the feces. It must be remembered, however, that, after a second treatment using the same therapeutic schedule, no change in the number of trichuris eggs was observed.

As concerns strongyloidosis, the percentages of cure obtained did not prove significant, since similar results could be observed in the control group, to which no treatment was provided.

When experimenting with new anti-helminthic compounds a control group must always be included for reference. In fact, some misleading interpretation may thus be avoided, as occurred in the present study, when a percentage of about 30% of apparent cure for ancylostomiasis, strongyloidosis and enterobiasis was observed in the control group.

Parasitological tests carried out by Kato's method always revealed a larger number of parasitized patients, especially with regard to mild infections. Such method has demonstrated to be an invaluable help for the assessment of drug therapy and may, perhaps, account for the divergencies in the percentages of cure achieved by other investigators.

Further experiments should be performed, especially with an aim to solve the problem of trichuriasis and to study the action of the drug in both isolated and associated parasitoses, as has recently been pointed out by RODRIGUES & MARTIRANI¹⁰.

Due to its low toxicity, great tolerability, wide range of action and easy administration, — pyrantel pamoate — which should also be tried in mass treatment — is indeed an invaluable weapon for the fight against intestinal parasitoses.

RESUMO

Estudos clínicos com pamoato de pirantel nas parasitoses intestinais

Foram tratados 127 pacientes portadores de diversas helmintíases intestinais com pamoato de pirantel, nas doses de 10 mg/kg/dia X 1, 10 mg/kg/dia X 3, 20 mg/kg/dia X 2 e 20 mg/kg/dia X 3, por via oral. O controle parasitológico foi realizado usan-

do-se os métodos quantitativos de Kato e Stoll, método de Graham (fita gomada) e Bearmann. Para recuperação dos ancilostomídeos e *Trichuris* eliminados, foi feita a tamização das fezes de 24 horas, em 4 dias sucessivos.

Com o esquema de 10 mg/kg/dia X 1 obteve-se 100,0% de cura para ascariíase e 84,6% para enterobíase. Com a dose total de 30, 40 e 60 mg/kg, os percentuais de cura na ancilostomíase foram de 57,1, 75,0 e 88,8%, respectivamente. Com os esquemas utilizados a droga mostrou atividade parcial contra *Trichuris*. Nos pacientes portadores de ancilostomídeos e *Trichuris*, onde não houve cura total das parasitoses, foi observada acentuada redução no número médio de ovos por grama de fezes e também a eliminação de vermes pelas fezes.

Num grupo de 11 pacientes tratados com 20 mg/kg/dia X 2, obteve-se 75,0% de cura na ancilostomíase e 42,8% na trichuriase. Trinta dias após, foi novamente administrada a mesma dose. O controle parasitológico realizado 28 dias após este segundo tratamento, não mostrou nova diminuição do número médio de ovos de *Trichuris* nas fezes e apenas 2 pacientes eliminaram vermes. Todavia, os 3 pacientes portadores de ancilostomídeos tiveram os exames coprológicos negativos.

Com relação ao *Strongyloides stercoralis*, nenhuma ação terapêutica pôde ser observada.

A tolerância ao produto foi boa, sendo que apenas cinco pacientes apresentaram diarreia, e dois outros vômitos, no dia seguinte à 1.^a dose.

Dada a baixa freqüência de efeitos colaterais e a alta eficácia do pamoato de pirantel, anti-helmíntico polivalente, esta droga deverá ser testada no tratamento em massa nas parasitoses intestinais.

ACKNOWLEDGMENTS

Thanks are expressed to Dr. Gildo Del Negro, Medical Director Pfizer Laboratories, Brazil, for the generous supply of pyrantel pamoate and the information concerning this compound. The Authors are indebted to Gercy de Souza Moraes and Oswaldo de Souza Moraes for their technical assistance.

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