

## CLINICAL TRIALS WITH PYRANTEL PAMOATE ON INTESTINAL HELMINTHS ON URBAN AND RURAL AREAS

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### SUMMARY

Ninety-seven ankylostomiasis and trichuriasis patients (38 of them living in urban areas and 59, in an endemic rural zone) have been treated with pyrantel pamoate obeying different schedules. Parasitological control was performed by Kato's and Stoll's quantitative methods, before treatment, and on the 13th-14th and 20th-21st days after it. As regards ankylostomiasis patients living in town and treated with total doses of 90-or100 mg and 40 mg per kg of body weight of the drug, the percentages of cure obtained were 100% and 70%, respectively. In this group, the decrease in the number of eggs in feces was around 90%. Trichuriasis patients treated with total doses of 40, 90 and 100 mg/kg presented percentages of cure of 0, 8 and 20%, respectively, the reduction in the number of eggs in feces being 40% with all schedules. As to the ankylostomiasis patients living in the endemic area and treated with total doses of 40 mg/kg, the percentages of cure obtained were 20% and 7%, respectively, when the total amount of the drug was divided into two daily doses or taken as a single one. The decrease in the number of eggs was around 60%. A hypothesis that the pyrantel pamoate is not active against ankylostomidae larval forms was put forth and, later on, experimentally demonstrated on *Nematospiroides dubius*. Considering the rare occurrence of side-effects, and good therapeutical activity, pyrantel pamoate must be tried for mass treatment aiming at the control of ankylostomiasis, provided that it can be periodically administered.

### INTRODUCTION

Clinical trials carried out with pyrantel pamoate by BUMBALO et al.<sup>3</sup>, DESOWITZ et al.<sup>5</sup>, AMATO NETO et al.<sup>1</sup>, YOKOGAWA et al.<sup>13</sup>, LEVI et al.<sup>8</sup>, RODRIGUES & MARTIRANI<sup>11</sup>, demonstrated this compound to be active in ascariasis, enterobiasis and ankylostomiasis.

KATZ et al.<sup>7</sup> showed that, as regards ankylostomiasis, by using total doses of 30, 40 and 60 mg of the drug per kg of body weight, the percentages of cure obtained were respectively 57.1, 75.0 and 88.8%. The same Authors also reported that, at these doses, the drug displayed only partial activity against *Trichuris trichiura*.

Some doubt still persists, however, as to the best therapeutic schedule for ankylostomiasis and trichuriasis, as well as to the effectiveness of such schedules in ankylostomiasis patients living in an urban area as compared with those from an endemic rural area.

This paper presents the results obtained, with pyrantel pamoate, in clinical treatment of town patients parasitized with hookworms and whipworms as well as of ankylostomiasis patients in an endemic rural area.

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#### MATERIAL AND METHODS

Ninety-seven patients (male and female) have been treated, 59 of them being children (aged 5 to 15 years) and the remaining 38, adults (aged 16 to 21 years). The former patients lived in a rural area (Calciolandia, MG, Brazil) and the latter ones, at the Instituto Berenice Martins Prates, Belo Horizonte, Brazil. All of them showed good clinical conditions.

#### *Therapeutic Schedules*

GROUP A — 10 patients living in urban areas, and parasitized with Ancylostomidae and *Trichuris trichiura*, were treated, *per os*, with a dose of 20 mg of pyrantel pamoate per kg of body weight (kg.b.w.), for two consecutive days.

GROUP B — 13 patients' urban areas, with Ancylostomidae and *Trichuris trichiura*, were administered 15 mg/kg.b.w., bid x 3.

GROUP C — 15 town patients presenting Ancylostomidae and *Trichuris trichiura* infection, received 10 mg/kg.b.w., bid x 5.

GROUP D — 31 children, living in a rural area and parasitized with Ancylostomidae, were treated with 10 mg/kg.b.w., bid x 2.

GROUP E — 28 children (selected in the same way as those picked out for group D) received, for 2 consecutive days, 20 mg/kg.b.w.

GROUP F — 21 children from groups D and E, not getting cured, resumed treatment, 30 days after the end of the first administration of the drug, under the schedule of 20 mg/kg.b.w. x 2.

To groups A, E and F, the drug was administered only in the morning, after breakfast; groups B, C and D also received treatment in the afternoon. All patients under treatment used the drug as tablets.

#### *Parasitological Control*

The evaluation of the drug efficacy was performed through the quantitative copro-parasitological methods of KATO<sup>9</sup> and STOLL<sup>10</sup> (groups A, B and C) or just through Stool's (groups D, E and F).

Before treatment, two parasitological tests were performed but, after treatment, tests were carried out on the 13th, 14th, 20th and 21st days; as to group F, tests were performed only on the 13th and on the 14th days. The mean number of eggs presented on Tables I to VI refer to the data from two successive stool examinations. After treatment, patients presenting negative Stoll examination were considered cured. Concerning groups B and C, whose patients received the largest doses of the drug, blood examinations were also performed (hemoglobin — Hb., hematocrit — Hct., leukocyte — Leuk., serum glutamic oxaloacetic transaminase — SGOT, serum glutamic pyruvic transaminase — SGPT) before and 7 days after treatment.

#### RESULTS

GROUP A — As regards ankylostomiasis and trichuriasis, the percentages of cure have been, respectively, 70.0 and 0.0.

Ankylostomiasis patients not cured after treatment presented, however, a decrease of about 90% in the mean number of eggs in their feces, as demonstrated by both Kato's and Stoll's methods (Table I).

Concerning trichuriasis, such decrease was seen to be, 14 and 21 days after the end of treatment, of 49.4 and 46.4%, respectively, by Stoll's methods, whereas, by Kato's technique, no decrease could be observed (Table I).

GROUP B — The percentages of cure, two and three weeks after treatment, have been 92.3 and 100.0 for ankylostomiasis and, for trichuriasis, 7.7 and 0.0, respectively.

There has been observed a decrease of about 50% in the mean number of eggs eliminated by *T. trichiura* patients observed not to be cured 20-21 days after treatment (Table II).

GROUP C — Regarding patients treated with 20 mg/kg/day x 5, the percentages of cure obtained were 100.0, in ankylostomiasis, and 20.0, in trichuriasis.

With regard to trichuriasis patients, when cure was not achieved, a decrease of about 40% in the mean number of eggs per gram

TABLE I

Fluctuation in the total and mean number of eggs from the feces of 10 patients treated with pyrantel pamoate at dose level of 20 mg/kg/day × 2 (Group A)

| Helminth                           |       | Ancilostomidae              |            |            | <i>T. trichiura</i> |            |            |            |
|------------------------------------|-------|-----------------------------|------------|------------|---------------------|------------|------------|------------|
| Treatment                          |       | Before                      | After      |            | Before              | After      |            |            |
|                                    |       |                             | 13-14 days | 20-21 days |                     | 13-14 days | 20-21 days |            |
| Copro-parasitological Examinations | Kato  | Total no. of eggs/g         | 18,280     | 881        | 771                 | 8,649      | 9,387      | 9,495      |
|                                    |       | No. of patients             | 10         | 3          | 3                   | 9          | 9          | 9          |
|                                    |       | Mean no. of eggs/g/patients | 1,828      | 294(83.9)  | 257(85.9)           | 961        | 1,043(0.0) | 1,055(0.0) |
|                                    | Stoll | Total no. of eggs/g         | 54,600     | 400        | 400                 | 6,012      | 2,700      | 3,400      |
|                                    |       | No. of patients             | 10         | 1          | 2                   | 9          | 8          | 8          |
|                                    |       | Mean no. of eggs/g/patients | 5,460      | 400(92.7)  | 200(96.3)           | 668        | 338(49.4)  | 425(36.4)  |

( ) — Percentage of reduction

TABLE II

Fluctuation in the total and mean number of eggs from the feces of 13 patients treated with pyrantel pamoate at the dose level of 30 mg/kg/day × 3 (Group B)

| Helminth                           |       | Ancilostomidae              |            |            | <i>T. trichiura</i> |            |            |           |
|------------------------------------|-------|-----------------------------|------------|------------|---------------------|------------|------------|-----------|
| Treatment                          |       | Before                      | After      |            | Before              | After      |            |           |
|                                    |       |                             | 13-14 days | 20-21 days |                     | 13-14 days | 20-21 days |           |
| Copro-parasitological Examinations | Kato  | Total no. of eggs/g         | 4,660      | 71         | 0                   | 6,071      | 7,116      | 4,186     |
|                                    |       | No. of patients             | 10         | 1          | 0                   | 13         | 12         | 13        |
|                                    |       | Mean no. of eggs/g/patients | 466        | 71(84.8)   | 0(100.0)            | 467        | 593(0.0)   | 322(45.7) |
|                                    | Stoll | Total no. of eggs/g         | 13,992     | 0          | 0                   | 6,600      | 5,400      | 1,896     |
|                                    |       | No. of patients             | 12         | 0          | 0                   | 12         | 9          | 8         |
|                                    |       | Mean no. of eggs/g/patients | 1,166      | 0(100.0)   | 0(100.0)            | 550        | 600(0.0)   | 237(56.9) |

( ) — Percentage of reduction

TABLE III

Fluctuation in the total and mean number of eggs from the feces of 15 patients treated with pyrantel pamoate at dose level of 20 mg/kg/day × 5 (Group C)

| Helminth                           |       | Ancilostomidae              |            |            | <i>T. trichiura</i> |            |            |           |
|------------------------------------|-------|-----------------------------|------------|------------|---------------------|------------|------------|-----------|
| Treatment                          |       | Before                      | After      |            | Before              | After      |            |           |
|                                    |       |                             | 13-14 days | 20-21 days |                     | 13-14 days | 20-21 days |           |
| Copro-parasitological Examinations | Kato  | Total no. of eggs/g         | 1,452      | 0          | 0                   | 9,375      | 4,320      | 4,968     |
|                                    |       | No. of patients             | 11         | 0          | 0                   | 15         | 12         | 12        |
|                                    |       | Mean no. of eggs/g/patients | 132        | 0(100.0)   | 0(100.0)            | 625        | 360(42.4)  | 414(33.8) |
|                                    | Stoll | Total no. of eggs/g         | 9,594      | 0          | 0                   | 10,245     | 2,898      | 3,200     |
|                                    |       | No. of patients             | 13         | 0          | 0                   | 15         | 6          | 5         |
|                                    |       | Mean no. of eggs/g/patients | 738        | 0(100.0)   | 0(100.0)            | 683        | 483(29.3)  | 640(6.3)  |

( ) — Percentage of reduction

TABLE IV

Fluctuation in the total and mean number of eggs from the feces of 31 patients treated with pyrantel pamoate at dose level of 10 mg/kg b.i.d. × 2 (Group D)

| Helminth                           |       | Ancilostomidae              |            |             |             |
|------------------------------------|-------|-----------------------------|------------|-------------|-------------|
| Treatment                          |       | Before                      | After      |             |             |
|                                    |       |                             | 13-14 days | 20-21 days  |             |
| Copro-parasitological Examinations | Stoll | Total no. of eggs/g         | 290,067    | 104,988     | 80,960      |
|                                    |       | No. of patients             | 31         | 26          | 22          |
|                                    |       | Mean no. of eggs/g/patients | 9,357      | 4,038(56.9) | 3,680(60.7) |

( ) — Percentage of reduction

of feces was observed, by Kato's method, whereas, by the that of Stoll, such percentages were found to be 29.3 and 6.3 (Table III).

*Blood examination*

Laboratory tests of patients in groups B and C (Hb, Hct, Leuk, SGOT and SGPT) did not show significant differences between the data obtained before and after treatment.

GROUP D — As to ankylostomiasis, the percentages of cure observed in this group, were about 20%.

As shown on Table IV, the decrease in the mean number of eggs in the feces of patients not cured was around 60.0%.

GROUP E — After treatment, the rate of cure of ankylostomiasis patients in this group was just 7.1%. The reduction in the mean number of eggs in the feces of patients not cured was about 60% (Table V).

GROUP F — Patients from groups D and E, observed not to be cured after the first course of treatment under the schedule of

20 mg/kg/day x 2, resumed treatment with the drug. After this second course, only a reduction of 42.8% in the number of ankylostome eggs could be observed (Table V).

*Side effects*

The side effects observed were abdominal pain (9 patients), diarrhea (2), nausea (2) and pyrosis (2). Such symptoms, however, were reported only by patients from groups B and C and lasted less than 24 hours.

DISCUSSION

In trichuriasis, the percentages of cure obtained with the therapeutic schedules reported have never been higher than 20%, as demonstrated by Kato's method, despite a decrease of 50% in the number of parasite eggs.

This confirms the findings of KATZ et al.<sup>7</sup> and RODRIGUES & MARTIRANI<sup>11</sup>, who demonstrated that the compound exhibit only partial action against this helminth.

The data obtained with pyrantel pamoate in the treatment of ankylostomiasis show that

TABLE V

Fluctuation in the total and mean number of eggs from the feces of 28 patients treated with pyrantel pamoate at dose level of 20 mg/kg/day x 2 (Group E)

| Helminth                       |       | Ancilostomidae                        |            |                        |             |
|--------------------------------|-------|---------------------------------------|------------|------------------------|-------------|
|                                |       | Before                                | After      |                        |             |
| Treatment                      |       |                                       | 13-14 days | 20-21 days             |             |
|                                |       | Copro-parasitological<br>Examinations | Stoll      | Total no. of<br>eggs/g | 261,996     |
| No. of patients                | 28    |                                       |            | 26                     | 25          |
| Mean no. of<br>eggs/g/patients | 9,357 |                                       |            | 4,038(56.9)            | 3,680(60.7) |

( ) — Percentage of reduction

TABLE VI

Fluctuation in the total and mean number of eggs from the feces of 21 patients treated twice with pyrantel pamoate at dose level of 20 mg/kg/day × 2 (Group F)

| Helminth                           |       | Ancilostomidae              |                  |             |
|------------------------------------|-------|-----------------------------|------------------|-------------|
| Treatment                          |       | Before 2nd Treatment        | After 13-14 days |             |
| Copro-parasitological Examinations | Stool | Total no. of eggs/g         | 42,987           | 24,591      |
|                                    |       | No. of patients             | 21               | 21          |
|                                    |       | Mean no. of eggs/g/patients | 2,047            | 1,171(42.8) |

( ) — Percentage of reduction

doses of 40, 90 and 100 mg, per kg of body weight, induce percentages of cure of 70, 100 and 100%, respectively. It must be pointed out that, under the first schedule of treatment, non-cured patients presented a decrease of about 90% in the number of eggs in feces. These results are consistent with those of KATZ et al.<sup>7</sup>, who reported this drug to be very effective when administered to patients, with mild and severe ankylostome infections, not living in contaminate areas.

The results obtained in patients living in endemic areas were by far, less satisfactory. In fact, a therapeutic schedule of 20 mg/kg of body weight, administered for 2 consecutive days, provided a percentage of cure around 20%, and a 60% decrease in the number of eggs. Non-cured patients, after a second course of treatment, presented a 40% decrease in the number of eggs in their feces.

The data regarding ankylostomiasis patients living in endemic areas suggest that the compound is ineffective against the parasite's larval tissue forms. In such areas, where constant re-infections occur, only the adult worms, present in the patient's intestine, are eliminated. The larval forms parasitizing

the tissues at the time of drug administration soon get to the worm's usual habitat, the intestine, and then start laying eggs. Similar results were also obtained when mebendazole and bitoscanate were used (unpublished data).

This fact could be experimentally demonstrated in albino mice infected with *Nematospiroides dubius*. Pyrantel pamoate was administered (100 mg/kg b.w., single dose, *per os*) to groups of 5 mice infected with 100 *N. dubius* larvae, on the 1st, 3rd, 5th, 7th, 10th and 14th days after infection. This dose was reported by HOWES & LINCH<sup>6</sup> as capable of curing 100% of infected mice, when the drug was administered 14 days after infection. All animals were sacrificed 18 days after infection.

The data obtained (Fig. 1) clearly show the inefficacy of the compound against the larval tissue forms of the parasite. In fact, the reduction of about 95-99% in the number of worms was achieved when the drug was administered on the 10th and 14th days of infection. On the 5th and 7th days, the reduction was about 25%. Mice treated on the 3rd day after infection did not show any change in the number of worms, as

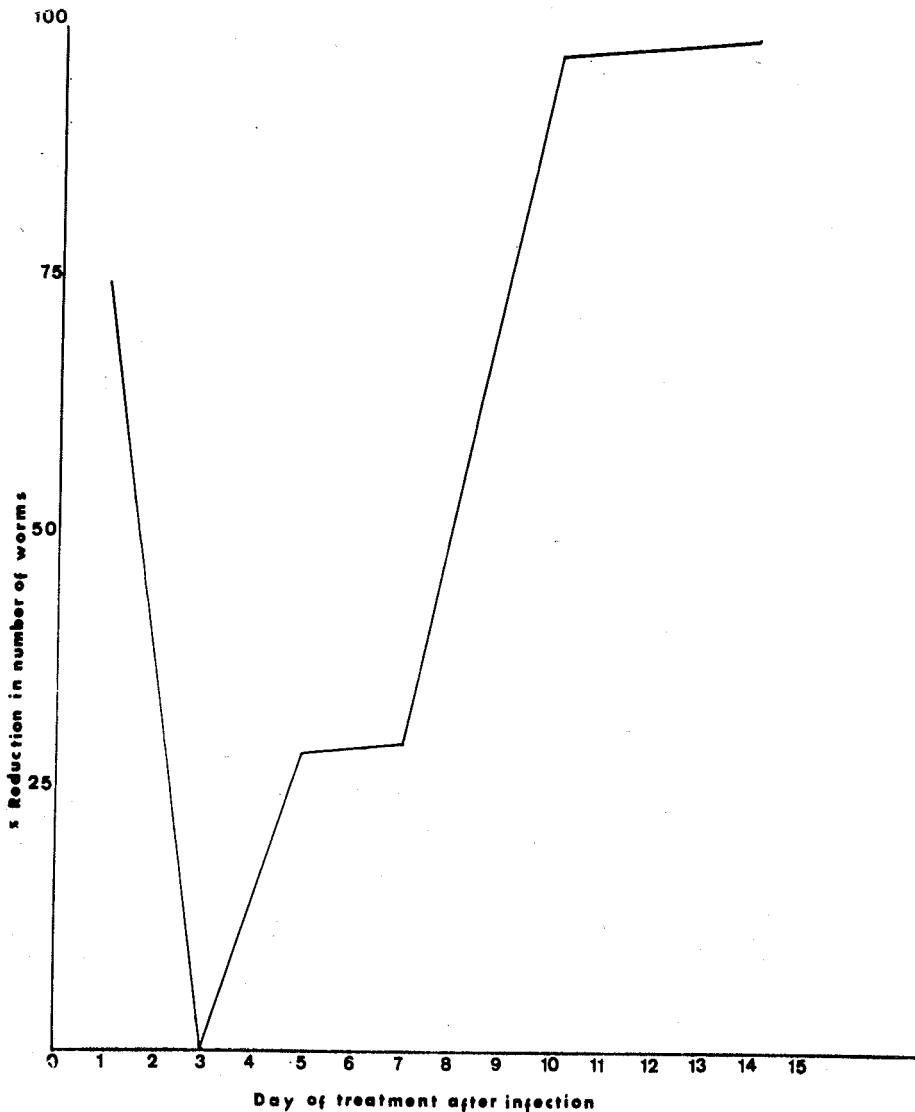


Fig. 1 — Percentage of reduction in the number of worms, from mice experimentally infected with *N. dubius*, and treated on different days after infection with single dose of pyrantel pamoate (100mg/kg, *per os*)

compared with those of the control group. The decrease of 75% in the number of worms in mice treated on the 1st day after infection indicates that larvae which had remained in the intestinal lumen had already been eliminated by the drug. This results were quite similar to that obtained by CORNWELL & BLORE<sup>4</sup>. It must be pointed out that, unlike *Necator americanus* and *Ancylostoma duodenale*, *N. dubius* does not

undergo the pulmonary cycle, despite being used as the biological model for the screening of drugs against ankylostomiasis. There must also be remarked that, in the average, *N. dubius* tissue cycle lasts about 8 days (STANDEN<sup>12</sup>).

When treating patients in ankylostomiasis endemic areas, the problem of constant re-infection should not be overlooked. As regards hookworm control, other schedules for drug

administration should be investigated and mass treatment trials be carried out by repeated therapeutic schedules at 30-60 day intervals, for a minimum period of one year. Such schedule, followed by BIAGI & RODRIGUES<sup>2</sup> in the treatment of ascariasis with piperazine, allowed the control of the helminthiasis at a small locality in Mexico. It is highly advantageous to use such schedule with pyrantel pamoate, which is simultaneously active against ascariasis, ankylostomiasis and enterobiasis. Probably, for economical reasons, such project will not be put into practice in all Brazilian endemic areas. Nevertheless, it is advisable that effective control of such helminthiasis be achieved in some enclosed agricultural areas, where ankylostomiasis is the primary cause of significant decrease in man's capacity and productivity.

#### RESUMO

##### *Ensaio clínico com pamoato de pirantel em helmintoses intestinais, em zonas urbana e rural*

Foram tratados com pamoato de pirantel 97 pacientes com ancilostomíase e tricuriíase, sendo 38 moradores em zona urbana e 59 em zona endêmica (rural). Os esquemas empregados em zona urbana foram 20 mg/kg/dia x 2, 30 mg/kg fracionado em 2 doses diárias durante 3 dias e 20 mg/kg/dia, fracionado em 2 doses, por 5 dias. Em zona rural foram utilizados 20 mg/kg/dia, dividido em 2 doses durante 2 dias e 20 mg/kg/dia x 2.

Foram realizados exames laboratoriais (hemoglobina, hematócrito, leucócitos e transaminases) antes e 7 dias após o tratamento, nos grupos tratados com dose total de 90 e 100 mg/kg, não tendo sido detectadas alterações significativas.

O controle parasitológico foi realizado utilizando-se os métodos quantitativos de Kato e Stoll, antes, no 13-14.º e 20-21.º dias após o tratamento.

Em vista dos resultados diferentes obtidos quando foram tratados pacientes em zona com ou sem transmissão ativa, foi levantada a hipótese de que o pamoato de pirantel não agiria sobre formas larvárias dos ancilosto-

mídeos. Este fato pode ser demonstrado experimentalmente utilizando-se o modelo biológico camundongo-*Nematospiroides dubius*.

Dada a baixa freqüência de efeitos colaterais e atividade terapêutica observados, o pamoato de pirantel deve ser ensaiado no tratamento em massa visando o controle de ancilostomíase, desde que usado em doses repetidas.

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