An Evaluation of Levamisole for Treatment of Ascariasis

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ABSTRACT: Levamisole (Decaris, Belgium) was tested in Iran, Brazil, and in Mississippi and Louisiana for its efficacy as a single-dose oral treatment for *Ascaris* infections. Subjects were children ages 2 to 15 years, and numbers treated with levamisole and comparative anthelmintics are as follows: 453 with levamisole; 461 with piperazine citrate; 17 with pyrantel pamoate; and 19 with a placebo. Cure rates and total reduction in mean egg counts observed were 92% and 98% respectively for levamisole and 66% and 90% for piperazine. Sixteen of 17 treated with pyrantel pamoate were cured. In none of the drugs were there notable side reactions, but in all four studies side effects were more frequent with piperazine than with levamisole. Levamisole was found to be a well-tolerated, highly effective single-dose ascaricide. It should prove to be particularly useful for mass chemotherapy in *Ascaris* control programs.

STUDIES with levamisole (Decaris, Belgium), the laevo-isomer of tetramisole, indicate it to be a highly effective single-dose oral anthelmintic for *Ascaris* and *Trichostrongylus* and suggest possible activity against hookworms.[1-7] The drug, through inhibition of dehydrogenase succinate in nematode muscle, paralyzes the worms and they are eliminated by peristalsis.[8] Levamisole is well tolerated by patients in dosages used for treatment of helminth infections and was shown to have no adverse effect on hemoglobin levels, blood urea, serum bilirubin, and liver function.[3]

We present results of studies conducted at four different geographic locations comparing the efficacy of levamisole versus piperazine citrate as single-dose ascaricides. Additional limited data were obtained on single-dose treatment with pyrantel pamoate for ascariasis and with levamisole for hookworm and whipworm infections.

MATERIALS AND METHODS

Subjects Studied

A total of 950 subjects for whom adequate follow-up studies were completed are included in the study. The number of patients treated is somewhat larger. The studies involved children from 2 to 15 years of age. They were selected at rural schools near Isfahan in Iran and near Belo Horizonte in Brazil and at public health clinics in rural areas in Mississippi and Louisiana within a 75-mile radius of New Orleans. They were fairly evenly divided between males and females except in Iran where males outnumbered females about 7:1.

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Ascaris Infections

In all four studies, subjects were selected on the basis of finding *Ascaris* eggs in direct fecal smears prepared by the Beaver egg-counting technic.[9] The degree of infection was established for each patient before treatment by doing two egg counts on each of two stool specimens passed at least 48 hours apart. To evaluate the effects of the drug, stools were examined between three to six weeks after treatment. Two stool specimens passed at least 48 hours apart were collected and two egg counts were done on each. If no eggs were seen on fecal smears, the specimen was examined by the zinc sulfate concentration technic. Infection loads were classified on the basis of eggs per gram of stool (epg) as follows: Light, less than 10,000 epg; medium, 10,000 to 49,999 epg; heavy, 50,000 or more epg. As minor deviations from the protocol, in fewer than 5% of patients the two pretreatment or posttreatment stool specimens for egg counts were not collected and, in these, results are based on counts made on a single stool. Further, in the Brazil study the zinc sulfate technic was inadvertently omitted for posttreatment stools found negative for *Ascaris*. The Louisiana study protocol included two additional groups, one for treatment with pyrantel pamoate and the other with a placebo.

Levamisole was administered in tablet form in one oral dose as follows:

10-20 kg body weight—50 mg (one tablet)
20-40 kg body weight—100 mg (two tablets)
Over 40 kg body weight—150 mg (three tablets)

Piperazine citrate was administered as a liquid in one oral dose of 150 mg/kg body weight to a maximum of 3.5 gm. *Pyrantel pamoate* was given in liquid form in one oral dose of 11 mg/kg body weight to a maximum of 1.0 gm. The *placebo* was administered in tablet form identical in appearance with a levamisole tablet but lacking the active ingredient. Drug administration for all subjects was supervised by members of the study teams.

RESULTS

The combined results for cure and egg-reduction rates achieved with levamisole and piperazine respectively are summarized in Table 1. Of 453 infected children treated with levamisole, 415 or 92% were cured. Piperazine cured 302 or 66% of 461. Overall egg-reduction rates were 98% and 90% for levamisole and piperazine respectively. There was some variation in results achieved by the different studies but, in all, cure rates and egg-reduction rates were consistently higher for levamisole than for piperazine. With the

TABLE 1. Ascariasis Cure Rates and Egg-Count Reductions in All Subjects Treated With Levamisole and Piperazine in Iran, Brazil, and the United States

Study Site	Cure Rates: Levamisole Number*	%	Piperazine Number*	%	Egg Reduction Rates: Levamisole epg†	%	Piperazine epg†	%
Iran	172/192	90	155/206	75	1300/80900	99	2400/83600	97
Brazil	197/207	95	124/214	58	700/32800	98	8600/35000	75
Mississippi	20/28	71	13/26	50	2200/59700	96	9300/54000	83
Louisiana	26/26	100	10/15	67	0/37200	100	2100/18500	89
Total	415/453	92	302/461	66	900/54900	98	5700/57200	90

*Number cured/number treated.
†Mean number of epg for study group after/before treatment.

exception of the Mississippi study, where only 71% were cured, cure rates with levamisole were at least 90%; for piperazine cure rates varied from 50% to 75%.

Table 2 compares the cure rates obtained among groups with differing infection loads treated with these drugs in each of the four studies. It may be seen that while in each study, infection densities for groups treated with either *levamisole* or *piperazine* were roughly comparable, between studies they showed considerable variation. Most intense infections occurred in Iran where about 60% of the subjects showed heavy infections with an average of more than 80,000 epg for both treatment groups. In Brazil infection densities were much lower, with about 17% of subjects showing heavy infections, the average counts being 32,800 and 35,000 epg for the two treatment groups. Children in Mississippi showed heavier worm burdens than those in Louisiana, with roughly 40% of the former versus 15% of the latter falling into the heavy infection category. This is reflected in the average egg counts which for levamisole and piperazine groups, respectively, were 59,700 and 54,000 epg for Mississippi and 37,200 and 18,500 epg for Louisiana.

The results of the Louisiana study, where two additional groups were treated, one with pyrantel pamoate and the other with a placebo, are presented in Table 3. All 26 children treated with levamisole and all but one of 17 treated with pyrantel pamoate were cured. Children treated with piperazine showed a 67% cure rate, while 17 of the 19 receiving a placebo continued to pass eggs.

In the Louisiana study 23 children treated with levamisole for ascariasis also harbored *Trichuris trichiura* (whipworm) as did nine children who received a placebo. Of the 23 treated with levamisole only one light infection was negative for whipworms on posttreatment stool examination, while one child with a negative examination before treatment showed a few eggs after treatment. Most egg counts were light to moderate and the average count of 5,300 epg before treatment was reduced to 4,300 epg after treatment. Among the nine children receiving placebo, two had no whipworms after treatment, and pretreatment and posttreatment counts were 6,781 and 6,139 epg respectively.

In the Mississippi study 19 children treated with levamisole for ascariasis also were infected with *Necator americanus* (hookworms). Results of posttreatment

TABLE 2. Ascariasis Cure Rates With Levamisole and Piperazine in Subjects With Differing Worm Loads

	Infection Load*	Levamisole epg**	Levamisole Cure Rate†		Piperazine epg	Piperazine Cure Rate	
IRAN	Light	6100	13/14	(93%)	5000	8/12	(67%)
	Medium	30200	47/54	(87%)	28100	47/62	(76%)
	Heavy	111400	112/124	(90%)	116800	100/132	(76%)
	Average	80900	172/192	(90%)	83600	155/206	(75%)
BRAZIL	Light	4400	88/91	(97%)	4700	62/88	(70%)
	Medium	26700	74/79	(94%)	24500	47/91	(52%)
	Heavy	121600	35/37	(95%)	128100	15/35	(43%)
	Average	32800	197/207	(95%)	35000	124/214	(58%)
MISSISSIPPI	Light	5200	6/7	(86%)	2900	4/5	(80%)
	Medium	29700	8/10	(80%)	20900	7/11	(64%)
	Heavy	121600	6/11	(55%)	115500	2/10	(20%)
	Average	59700	20/28	(71%)	54000	13/26	(50%)
LOUISIANA	Light	5400	7/7	(100%)	6400	3/5	(60%)
	Medium	22200	13/13	(100%)	24500	7/10	(70%)
	Heavy	100400	6/6	(100%)	0	0	
	Average	37200	26/26	(100%)	18500	10/15	(67%)

*See text for interpretation of infection load categories.
**Mean number of epg for each subgroup.
†Number cured/number treated (% cured).

TABLE 3. Ascariasis Cure Rates and Egg-Count Reductions in All Louisiana Subjects Treated With Levamisole, Piperazine, Pyrantel Pamoate, and a Placebo

	Levamisole		*Pyrantel Pamoate*		*Piperazine*		*Placebo*	
Cure rates*	26/26	(100%)	16/17	(94%)	10/15	(67%)	2/19	(11%)
Egg reduction rates†	0/37200	(100%)	5400/54100	(90%)	2100/18500	(89%)	21200/24400	(13%)

*Number cured/number treated (% cured).
†Mean number of epg after/before treatment (% reduction).

stool examination showed all subjects still passing hookworm eggs. Mean egg counts before and after treatment were 4,800 epg and 4,100 epg, respectively.

Side effects of levamisole and piperazine citrate observed during this study are shown in Table 4. Of 489 treated with levamisole, 64 or 13% complained of one or more side reactions, while 108 or 22% of 498 treated with piperazine voiced such complaints. The more common complaints for both drugs included abdominal pain, headache, and nausea. Dizziness, vomiting, and diarrhea occurred, but much less frequently. The majority of complaints were mild and a few moderate, while severe complaints were rare. The numbers in each of the two studies in the United States are too small to be meaningful for evaluating side reactions. The combined results as presented in Table 4 are probably more valid and show that of 58 children treated with levamisole only two or 4% reported side effects, compared to six of 41 or 15% of those treated with piperazine.

DISCUSSION

Data presented in Tables 1 and 2 show that the groups tested with levamisole and piperazine respectively in each study were sufficiently similar in numbers and in intensity of infections to provide the basis for a valid comparison of their efficacy as ascaricides. In all four studies levamisole proved to be the more effective ascaricide, achieving uniformly excellent egg-reduction rates (96%-100%) and an average cure rate of 92%. We are unable to explain the difference between the 100% cure rate achieved in Louisiana with a 71% cure rate for Mississippi. Interestingly, the Mississippi subjects also showed the lowest cure rates for piperazine. These differences may be significant because drug administration as well as stool collections for both studies were supervised by the same individuals. The effectiveness of levamisole did not appear to be influenced by worm loads as there were no marked differences in cure rates for light, medium, or heavy infections in the four studies. The somewhat higher levamisole cure rates observed in Brazil (95%) as compared to Iran (90%) may be due to the fact that the zinc sulfate concentration was not done in Brazil, while in Iran an additional 12 positive results were found in posttreatment stools by this technic. In Mississippi the heavy infections showed a cure rate of 55% as compared to the 80% and 86% for the light and medium infected groups, but total numbers treated in this study are too small to provide valid comparisons.

Comparisons with pyrantel pamoate are available only in the limited Louisiana study which shows that levamisole is at least as effective as pyrantel pamoate for treatment of ascariasis.

Cure rates for piperazine showed a progressive decline with increasing worm loads in the Brazil and Mississippi studies. This did not occur in the Iran and Louisiana trials although in the latter the subjects were few and none showed heavy infections. It is puzzling that even though the average worm load in Iran (83,600 epg) was much higher than in Brazil (35,000 epg) both cure and egg-reduction rates were higher in Iran (75% and 97%) than in Brazil (58% and 75%). Because the results with levamisole in these two studies are so similar, the difference found with piperazine treatment cannot be explained on the basis of personnel and technical differences. These observations plus differences observed in results of the Louisiana and Mississippi treatment studies discussed above suggest the possible occurrence of variations in geographic strain susceptibility to ascaricides.

In the single dosages used in our limited studies there was no indication that levamisole was effective for treatment of *Necator* and *Trichuris*.

Side reactions were less frequent in children receiving levamisole than in those given piperazine. This was a consistent finding in all four studies (Table 4). There were marked differences in prevalence of side effects observed in subjects for the different countries. Thus, for levamisole and piperazine, respectively, side reactions were reported in 6% and 11% for Brazil, in 23% and 35% for Iran, and 4% and 15% for the United States. We do not have a simple explanation for this. A higher worm burden in Iran as compared to Brazil was considered a possible explanation. But analysis of all subjects with drug reactions in the four studies revealed

TABLE 4. Frequency of Side Effects Reported for Levamisole and Piperazine in Treating for Ascariasis in Iran, Brazil, and the United States

	Levamisole		*Piperazine*	
Study	*No. Treated*	*Number With Side Reactions*	*No. Treated*	*Number With Side Reactions*
Brazil	223	14 (6%)	238	25 (11%)
Iran	208	48 (23%)	219	77 (35%)
USA	58	2 (4%)	41	6 (15%)
	489	64 (13%)	498	108 (22%)

that such reactions occurred as frequently in low and medium intensity as in high intensity infections. Side reactions are for the most part subjective and undoubtedly influenced to a great extent by comments regarding untoward drug reactions made during drug administration. We believe, therefore, that there may be a question regarding the interpretation of our findings on drug reactions. On the other hand, there would appear to be little doubt that both drugs are relatively well tolerated and that piperazine causes more side reactions than levamisole. Because of its high efficacy, relative freedom from side effects and ease of administration, levamisole should be particularly useful for mass chemotherapy in *Ascaris* control programs.

References

1. Thienpont D, Brugmans J, Abadi K, et al: Tetramisole in the treatment of nematode infections in man. *Am J Trop Med Hyg* 18:520-525, 1969
2. Lionel NDW, Mirando EH, Nanayakkara JC, et al: Levamisole in the treatment of ascariasis in children. *Br Med J* 4:340-341, 1969
3. Hall SA, Joseph MM, Saggar SN, et al: A trial of Ketrax (the laevo-isomer of tetramisole) in the treatment of ascariasis. *E Afr Med J* 47:424-433, 1970
4. Huys J, Kayihigi J, Freyens P, et al: Treatment of *Ascaris* infections with levamisole. *Medikon* (2nd yr) Jan 1973, pp 15-17
5. Krubwa F, Gatti F, Lontie M, et al: Community wide periodic anthelmintic treatment with levamisole. *Ann Soc Belge Med Trop* 54:167-176, 1974
6. Chege SW, Gitoho F, Wanene GSN, et al: Single-dose treatment of hookworm in Muranga District. *E Afr Med J* 51:60-62, 1974
7. Arfaa F, Farahmandian I: Progress achieved in the chemotherapy of soil-transmitted helminths. Presented at 9th International Congress on Chemotherapy, London, 1975
8. Van den Bossche H, Janssen PAJ: The biochemical mechanism of action of the antinematodal drug tetramisole. *Biochem Pharmacol* 18:35-42, 1969
9. Beaver PC: The standardization of fecal smears for estimating egg production and worm burden. *J Parasitol* 36:451-456, 1950

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"Hawkeye Pierce had no interest in contributing to the morass of medical literature, to what he called the Journals of Unnecessary Research. But, now and then, he spent three consecutive nights writing about a case that interested, helped, or hurt him. . . . The *Maine Medical Journal,* like all minor and most major medical journals, is devoted to distillations of other medical writing, cloudy, meaningless investigations of subjects discussed clearly elsewhere or scientifically suspect analyses of rare cases." [1]

Hawkeye, as usual, has overstated the case but it's the kernel of truth in what he says that makes his satire so effective.

Reference

1. Hooker R: *M*A*S*H Goes to Maine.* New York, Pocket Books, 1973

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