

Anthelmintic Efficacy of Methyl-5-benzoylbenzimidazole-2-carbamate (Mebendazole) against Multiple Helminthic Infections

Byong-Seol Seo, Seung-Yull Cho, Shin-Yong Kang and Jong-Yil Chai

*Department of Parasitology and Institute of Endemic Diseases,
College of Medicine, Seoul National University*

INTRODUCTION

Mebendazole, methyl-5-benzoylbenzimidazole-2-carbamate, which was introduced by Actor et al. (1967), has been evaluated as a broad-spectrum anthelmintic, effective on human intestinal nematodes (Brugmans et al., 1971; Pena Chavarria et al., 1973; Sargent et al., 1974; Soh et al., 1974; Wolfe et al., 1974; Miller et al., 1974; Nagalingam et al., 1976; Islam et al., 1976) and adult or larval cestodes (Soh et al., 1974; Islam et al., 1976; Kammerer et al., 1976; Eckert et al., 1976). Toxicologic studies made by Marsboom (1973) revealed the high safety margin and good tolerance in a variety of laboratory and domestic animals. Furthermore, this drug was also proved to degenerate eggs of some nematodes morphologically both *in vivo* (Wagner & Pena Chavarria, 1974a) and *in vitro* (Banerjee et al., 1971; Wagner & Pena Chavarria, 1974b).

Recently, mebendazole was synthesized by the processes of Korean patent and is said to have been processed with particular consideration for the purified product. Present study was undertaken to evaluate the drug efficacy and safety of this drug upon rural Koreans with recommended dosage schedule against multiple intestinal helminthic infections.

MATERIALS AND METHODS

Inhabitants of the rural villages in Pochun Gun, Kyunggi Do(=Province) and Jinyang Gun, Kyungsang Nam Do were subjected to this evaluation during November to December, 1976.

A total of 288 fecal specimens was collected from the above villages for the examination of intestinal helminths. Eighty-five cases were separately examined by Scotch-tape anal swab for detection of *Enterobius vermicularis*. The cellophane thick smear technique was applied for the qualitative diagnosis of the above fecal specimens and Stoll's egg counting method was also employed for the quantitative evaluations before and after treatment.

The positive cases were treated with mebendazole (Korean Patent, supplied by Shinpoong Pharmaceuticals, Seoul), at the dose of total 600mg, which was divided by 100mg, twice daily for three days.

The cases infected with *E. vermicularis* were also treated with same dosage schedule. Three weeks after the last day of the drug administration, the stool examinations after treatment were conducted to evaluate the drug efficacy. The follow-up study of *E. vermicularis* infection was made by anal swab on the 21st day after

treatment.

Adverse effects during and after treatment were observed only upto 24 hours after the last administration of mebendazole.

RESULTS

The results of stool examination undertaken before treatment were shown in Table 1. Both of the two communities were highly endemic with soil-transmitted helminthic infections. The species of hookworms in these areas was identified as *Ancylostoma duodenale* through the

previous surveys.

The degree of multiple infections in these two communities was presented in Table 2, among followed-up cases.

The anthelmintic efficacy of mebendazole against *A. lumbricoides* infection was evaluated and presented in Table 3 and 4. Out of 168 egg positive cases, 158 were converted to egg negative (94.5%) on the 21st day after treatment and the egg reduction rate in 130 cases was 99.6%. There is almost no difference between data collected in two areas in each negative conversion and reduction rates.

Table 1. The results of stool examination before treatment in Pochun and Jinyang Gun, revealed by cellophane thick smear technique

	Pochun Gun		Jinyang Gun		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
No. examined	141		147		288	
No. of cases with negative	21	14.9%	6	4.1%	27	9.4%
<i>Ascaris lumbricoides</i>	91	64.5%	105	71.4%	196	68.1%
<i>Trichuris trichiura</i>	104	73.8%	109	74.1%	213	74.0%
Hookworm (= <i>A. duodenale</i>)	5	3.5%	28	19.0%	33	11.5%
<i>Trichostrongylus orientalis</i>	1	0.7%	21	14.3%	22	7.6%
<i>Clonorchis sinensis</i>	2	1.4%	62	42.2%	64	22.2%
<i>Metagonimus yokogawai</i>	8	5.0%	0	—	8	2.4%
<i>Hymenolepis nana</i>	2	1.4%	7	4.8%	9	3.1%
<i>Taenia saginata</i>	1	0.7%	0	—	1	0.3%

Table 2. Analysis of multiple infections of helminths

No. examined: 218

Combinations	Helminth(s)	No. cases	Total
Single infection	<i>A. lumbricoides</i>	19	46
	<i>T. trichiura</i>	26	
	<i>C. sinensis</i>	1	
Double infection	<i>T. trichiura</i> with other	91	103
	Other combinations	12	
Triple infection	<i>T. trichiura</i> with others	51	54
	Other combinations	3	
Quadruple infection	<i>T. trichiura</i> with others	14	14
	Other combinations	0	
Quintuple infection	<i>T. trichiura</i> with others	1	1
	Other combinations	0	

In case of *T. trichiura* infection, 213 cases were treated with recommended dosage of mebendazole, only 48 cases were found to be negative by cellophane thick smears after treatment (Table 3). The negative conversion rates were 28.0 and 26.6% (average 27.3 per cent) in two communities, and the egg reduction rate was 65.5% in average. It was revealed mebendazole is almost ineffective against *T. trichiura* infection in the recommended dose, although the treated cases are all lightly infected, whose mean E.P.G. was in the range of 300 to 400.

In hookworm infections, follow-up study was made on 28 out of 33 treated cases to evaluate the drug efficacy. As shown in Table 3 & 4, both of the negative conversion and egg reduction rates were 71.4 per cent and 97.3 per cent respectively.

Table 3. Cure rate of intestinal helminths in dose of 200mg/day for 3 days of mebendazole

Helminth	No. followed	No. cured	Cure rate (%)
<i>A. lumbricoides</i>	168	158	94.0
<i>T. trichiura</i>	176	48	27.3
<i>A. duodenale</i>	28	20	71.4
<i>T. orientalis</i>	20	19	95.0
<i>E. vermicularis</i> *	52	48	92.3
<i>C. sinensis</i>	53	1	1.9
<i>M. yokogawai</i>	6	0	—
<i>H. nana</i>	9	4	44.4

* Evaluated by anal swab separately.

Average 95.0 per cent of negative conversion rate was revealed on 20 followed-up cases infected with *Trichostrongylus orientalis* (Table 3 and 4).

In cases of *E. vermicularis* infection, forty-eight out of 52 positives were found negative by anal swabs three weeks after treatment.

Seventy-two cases out of intestinal parasites infections treated with mebendazole were found concomitantly infected with the trematodes, *Clonorchis* and *Metagonimus*. However, the efficacy of mebendazole upon these two kinds of trematodes were found to be negligible (Table 3).

The anthelmintic efficacy of mebendazole against *Hymenolepis nana* infection was also examined in nine cases. Four out of 9 cases were found negative through follow-up examination three weeks after treatment (Table 3).

One case of *Taenia saginata* infection was also found in this study. No eggs were found in stool examination on the 21st day after treatment, however, no further follow-up study was made.

During the course of treatment, side effects were encountered, mainly gastrointestinal troubles such as nausea, abdominal discomfort in two women cases and diarrhea in two children. Some adult *Ascaris* worms were expectorated through mouth and/or nasal opening of six heavily infected cases of children, whose E.P.G. was in the range from 100,000 to 200,000.

Table 4. Egg reduction rate of mebendazole against intestinal helminths

Helminths	Before treatment		After treatment		ERR* (%)
	No. followed	Sum of E.P.G.	No. positive	Sum of E.P.G.	
<i>A. lumbricoides</i>	130	1,883,200	5	8,400	99.6
<i>T. trichiura</i>	111	41,400	69	14,300	65.5
<i>A. duodenale</i>	22	11,000	3	300	97.3
<i>T. orientalis</i>	8	1,600	0	0	100

* ERR: Egg reduction rate

DISCUSSION

This study also confirmed that mebendazole is a satisfactory, broadspectrum anthelmintic, effective on *A. lumbricoides*, *A. duodenale*, *E. vermicularis* and *T. orientalis* in aspects of negative conversion, and egg reduction rate and the tolerance of the treated cases. But the results in cases of *T. trichiura* infection were unsatisfactory compared with so many previous reports which admitted the higher efficacy of mebendazole against this peculiar nematode inhabiting in colon.

Pena Chavarria et al. (1973) reported 75% of cure rate and 99.3% of egg reduction with three-day schedule against trichuriasis. Sargent et al. (1974) and Wolfe et Wershing (1974) also obtained 64.3% and 68.2% of cure rates and more than 87% of egg reduction rates on trichuriasis patients. Miller et al. (1974) agreed on above papers with the same dosage schedule.

Some of the reports were against the above-mentioned efficacy of mebendazole upon *T. trichiura* infections. Yokogawa et al. (1976) reported that only one of 6 treated cases turned to negative and egg reduction could be obtained only in 4 cases. Nagalingam et al. (1976) reported that three-day schedule of mebendazole in the treatment of mild, moderate and heavy infection cases of *T. trichiura* was insufficient to obtain the satisfactory cure and good results were obtained with three courses of repeated treatments, each course with 100mg twice daily for three consecutive days.

In this trial, the anthelmintic efficacy of mebendazole in the treatment of lightly infected cases with *T. trichiura* was so unsatisfactory, with negative conversion rate of 27.3% and egg reduction rate of 65.5%. Results from the two villages were almost similar. At the present study, it was considered that the recommended

dose of mebendazole in the treatment of *T. trichiura* infection is insufficient to obtain complete cure.

The unsatisfactory efficacy of mebendazole against *T. trichiura* infection may be resulted from strain difference in susceptibility and inadequate activity of the drug against this worm even in the light degree of worm burden, in the multiple infections with other helminths in the present study. Since the mebendazole of Korean product revealed, in general, satisfactory anthelmintic activity against other intestinal nematodes, the defects in product may not be considered as the reason of ineffectiveness on *Trichuris*. The strain difference and resistance of *T. trichiura* to this drug were not noted yet. The multiple infections seemed to influence the drug efficacy, because 26 single *T. trichiura* infection cases showed 42.3% of negative conversion rate and 157 mixed infection cases showed 24.9%. But statistically the difference was not significant.

From the above considerations, it was thought that the recommended dose of mebendazole was insufficient in the complete deworming of *T. trichiura* in multiple infected cases with intestinal helminthes.

SUMMARY

A clinical trial of Korean Patent mebendazole was undertaken upon some intestinal helminthic infections in 288 rural Koreans residing in Pochun and Jinyang Gun, from November to December, 1976. They were examined by the cellophane thick smear technique, Stoll's egg counting technique and/or Scotch-tape anal swab before and 3 weeks after the treatment. The administered dose of mebendazole was 600mg, divided by 100mg, twice daily for 3 consecutive days disregarding the body weight and the age of the cases.

It was confirmed that mebendazole is very

effective, broad-spectrum anthelmintic, especially against *Ascaris*, *Ancylostoma*, *Trichostrongylus* and *Enterobius* infections. Their negative conversion rate and egg reduction rate were respectively; 94.0 and 99.6 per cent in *Ascaris*, 71.4 and 97.3 per cent in *Ancylostoma* and 95.0 and 100 per cent in *Trichostrongylus*. The negative conversion rate in *Enterobius* was 92.3 per cent.

The anthelmintic efficacy against *T. trichiura* infection was not satisfactory in spite of low worm burden (negative conversion rate, 27.3%, egg reduction rate, 65.5%).

ACKNOWLEDGMENT

The present authors express their thanks to Shinpoong Pharmaceuticals Co. for providing Mebendazole used in this study.

REFERENCES

- Actor, P., E.L. Anderson, C.J. Dicuollo, R.J. Ferlauto, J.R.E. Hoover, J.F. Pagano, L.R. Ravin, S.F. Scheidy, R.J. Stedman and V.J. Theodorides (1967). New broad spectrum anthelmintic, methyl-5(6)-butyl-2-benzimidazole carbamate. *Nature*, 215 : 321-322.
- Banerjee, D., A. Mandal and O. Prakash (1971). Mebendazole (R-17,635) : a new anthelmintic in the development of hookworms. *Trans. Roy. Soc. Trop. Med. & Hyg.*, 65 : 685-686.
- Brugmans, J.P., D.C. Thienpont, I. Wijngaarden, O.F. Vanparijs, V.L. Schuermans and H.L. Lauwers (1971). Mebendazole in enterobiasis. Radiochemical and pilot clinical study in 1,278 subjects. *J. Am. Med. Assoc.*, 217 : 313-319.
- Eckert, J. and J. Pohlenz (1976). Zur Wirkung von Mebendazole auf Metazestoden von *Mesocostoides corti* and *Echinococcus multilocularis*. *Tropendmed. u. Parasit.*, 27 : 247-262.
- Islam, N and N.A. Chowdhury (1976). Mebendazole and pyrantel pamoate as broad-spectrum anthelmintics. *S.E. Asian J. Trop. Med. Publ. Hlth.*, 7:81-84.
- Kammerer, W.S. and D.M. Judge (1976). Chemotherapy of hydatid diseases (*Echinococcus granulosus*) in mice with mebendazole and bithionol. *Am. J. Trop. Med. & Hyg.*, 25: 714-717.
- Marsboom, S. (1973). Toxicologic studies on mebendazole. *Toxicol. & Appl. Pharmacol.*, 24:371-377.
- Miller, M.J., I.M. Krupp, M.D. Little and C. Santos (1974). Mebendazole, an effective anthelmintic for trichuriasis and enterobiasis. *J. Am. Med. Assoc.*, 230:1, 412-1, 414.
- Nagalingam, I., L.E. Lam, M.J. Robinson and A.S. Dissanaik (1976). Mebendazole in treatment of severe *Trichuris trichiura* infection in Malaysian children. *Am J. Trop. Med. & Hyg.*, 25:568-572.
- Pena Chavarria, A., J.C. Swartzwelder, V.M. Villarejos and R. Zeledon (1973). Mebendazole, an effective broad spectrum anthelmintic. *Am. J. Trop. Med. & Hyg.*, 22:592-595.
- Sargent, R.G., A.G., A.M. Savory, A. Mina and P.R. Lee (1974). A clinical evaluation of mebendazole in the treatment of trichuriasis. *Am. J. Trop. Med. & Hyg.*, 23:375-377.
- Soh, C.T., B.H. Lee, D.Y. Min, S.J. Chang and J.H. Lee (1974). Clinical trial of Vermox (Mebendazole), a new broad spectrum anthelmintic. *Yonsei Rept. Trop. Med.*, 5: 148-152.
- Wagner, E.D. and A. Pena Chavarria (1974a). *In vitro* effects of a new anthelmintic, mebendazole (R-17,635) on the eggs of *Trichuris trichiura* and hookworm. *Am. J. Trop. Med. & Hyg.*, 23:151-153.
- Wagner, E.D. and A. Pena Chavarria (1974b). Morphologically altered eggs of *Trichuris*

trichiura following treatment with mebendazole. Am. J. Trop. Med. & Hyg., 23:154-157.
Wolfe, M.S. and J.M. Wershing (1974). Mebendazole: Treatment of trichuriasis and ascariasis in Bahamian children. J. Am. Med.

Assoc., 230:1,408-1,411.
Yokogawa, M., M. Sano and K. Saito (1976). Anthelmintic efficacy of mebendazole for trichuriasis. Jap. J. Parasit., 25(1, Suppl.): 16,

＝國文抄錄＝

蠕蟲感染에 있어서의 國產 Mebendazole의 驅蟲效果

서울大學校 醫科大學 寄生蟲學敎室 및 風土病研究所
徐 丙 高・趙 昇 烈・姜 信 榮・蔡 鍾 一

메벤다졸製劑가 蛔蟲, 鉤蟲, 蟯蟲 및 鞭蟲感染에까지 좋은 驅蟲效果가 있으며 이런 線蟲類 感染뿐만 아니라, 無有鉤條蟲, 矮小條蟲 등의 條蟲類 感染에 對하여도 驅蟲效果가 있다는 것이 1970年 이대로 간 알려져 왔다. 著者 등은 韓國產 메벤다졸 製劑의 韓國人에 있어서의 安全度 및 그 驅蟲效果를 再確認하기 위하여 1976年 11月부터 12月까지 사이에 京畿道 抱川郡 및 慶南 晉陽郡의 各一個部落 住民 288名을 對象으로 메벤다졸 100mg씩을 1日 2回, 總 3日間 投與하고 投藥前 및 投藥後 3週의 大便檢査에 依하여 蟲卵陰轉率 및 蟲卵減少率을 調査하였다. 그 結果는 다음과 같다.

1. 蛔蟲感染者는 196名(68.1%)이었으며 追跡檢査를 끝마친 168名 中 158名(94.0%)이 蟲卵陰轉되고 蟲卵減少率은 99.6%이었다.
2. 鞭蟲感染者는 213名(74.0%)이었고, 追跡된 176名에서의 蟲卵減少率은 27.3%이었고, 蟲卵減少率은 65.5%이었다.
3. 鉤蟲感染者는 33名(11.5%)이었으며 追跡된 28名 中 蟲卵陰轉率은 71.4%, 蟲卵減少率은 97.3%이었다.
4. 東洋毛樣線蟲感染者(22名, 7.6%) 中 20名에서의 蟲卵陰轉率은 95%, 蟲卵減少率은 100%이었다.
5. 肛門周圍塗抹法에 依한 蟯蟲卵陽性者는 58名이었고 追跡된 52名에서의 蟲卵陰轉率은 92.3%이었다.
6. 肝디스토마 및 橫川吸蟲 感染者에 있어서의 蟲卵陰轉率 및 蟲卵減少率은 매우 낮아 이 吸蟲들에 對한 驅蟲效果는 없는 것으로 생각되었다.
7. 矮小條蟲感染者 9名 中 4名(44.4%)이 治療 3週後 蟲卵이 陰轉되었다.
8. 副作用으로 輕度の 腹痛, 惡心 등 胃腸管症狀이 4名에서 發見되었고, 蛔蟲卵의 E.P.G.가 100,000~200,000인 兒童中 6名에서 治療途中 蛔蟲의 成蟲이 입 또는 코로 排出되었다.