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Efficacy of Mebendazole in Treatment and Control of Trichuriasis in Korea

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INTRODUCTION

Trichuris trichiura infection is currently the most prevalent human helminthiasis in Korea. According to some recent nationwide or local surveys the egg positive rate ranged from 23 to 45% among the subjected inhabitants (Rim *et al.*, 1979; Ministry of Health and Social Affairs & Korea Association for Parasite Eradication, 1981; Seo *et al.*, 1981). If it is intended to control this infection nationwidely, many pilot studies on the control scheme, *etc.* are the prerequisites.

Mebendazole, a broad-spectrum anthelmintic, has been appreciated for its therapeutic action on *T. trichiura* infection (Pena Chavarria *et al.*, 1973; Soh *et al.*, 1974; Wolfe *et* Wershing, 1974; Miller *et al.*, 1974; Kim, 1975; Scragg *et* Proctor, 1977 & 1978; Lee *et* Lim, 1978). But the efficacy of mebendazole has sometimes been unsatisfactory and inconsistent by single 3-day course recommended regimen both in heavy and in light infection cases (Miller *et al.*, 1974; Iyngkaran *et al.*, 1976; Seo *et al.*, 1977; Scragg *et* Proctor, 1977 & 1978; Yokogawa, 1978; Kan, 1983).

However, it was reported that mebendazole has a strong inhibitory action on egg synthesis *in vivo* and egg development *in vitro* after the drug has contact with *T. trichiura* worms in human intestine (Wagner *et* Pena Chavarria, 1974 a & b; Paul *et* Zaman, 1975; Iyngkaran *et al.*, 1976; Wagner *et* Rexinger, 1978). Therefore, mebendazole is expected to be useful in the reduction of reinfection source after mass chemotherapy and finally to play a great role in control of trichuriasis in endemic areas.

This study was designed with two objectives. The first one was to re-evaluate the therapeutic efficacy of mebendazole on *T. trichiura* infection with variable dosage regimens. The second purpose was to test and compare the long term control efficacy of trichuriasis by mebendazole for one year period when used repeatedly at regular intervals, every 3, 6 and 12 months.

MATERIALS AND METHODS

1. Short-term Evaluation of the Drug Efficacy

A total of 627 egg positive cases of *T. trichiura* (436 from Gangjin Gun, Jeonla-nam Do, and 191 from Siheung Gun, Gyeonggi Do) were detected from the preliminary stool examinations in 1978 and 1982 in respective areas. They were divided into 8 groups and treated with various doses of mebendazole (Korean Product from Shinpoong Pharmaceutical Co.) (Table 1). Out of the treated cases, 430 responded to the follow-up stool examinations, qualitative and quantitative, performed 3 weeks after the drug admini-

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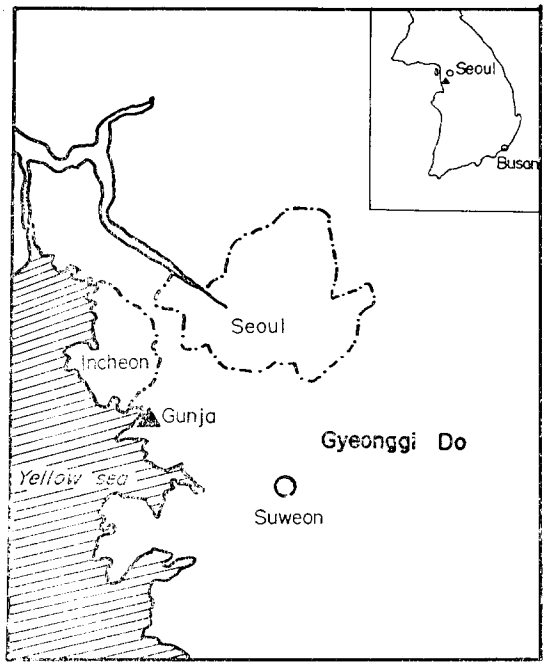

Fig. 1. Map showing the surveyed area for trichuriasis control, Gunja Myon, Siheung Gun, Gyeonggi Do, Korea.

stration. On the higher dose groups, the follow-up examination was repeated 7 weeks after the treatment to observe any delayed cure case (Table 2).

The qualitative stool examination was done by cellophane thick smear technique with single smear per case per examination. The quantitative examination was undertaken by Stoll's egg counting technique also one time per case. Repeated egg countings were done if eggs were found by cellophane smear but zero in egg counting.

The adverse effects by mebendazole during and after chemotherapy, if any, were observed until 24 hours after the drug administration.

2. Observation on the Efficacy of Trichuriasis Control

A rural village located in Gunja Myon, Siheung Gun, Gyeonggi Do, (Fig. 1), consisted of 551 inhabitants, was selected for this study. The pre-treatment stool examination on May, 1982 revealed 41.5% of egg positive rate of *T. trichiura*. The subjected village was divided into 4 small hamlet groups (Table 4) to compare the control efficacy by repeated mass chemotherapy at regular intervals.

Placebo (vitamin B complex) was given to Group I (every 3 months). A total of 600 mg mebendazole was given to Group II (every (every 3 months), III (every 6 months) and IV 12 months). The inhabitants of Group II were further divided into Group II-1 and II-2 according to regimens of mebendazole. In Groups II-1, III and IV, mebendazole was given in conventional regimen, 100 mg twice daily for 3 days, and in Group II-2, the drug was given in 600 mg single or two divided doses. The treatments were continued from May, 1982 to May, 1983 in all groups.

In each chemotherapy, blanket mass treatment method was applied to whole residing inhabitants lest there should be infected drop-outs. Follow-up examinations were done to observe the changing pattern of the prevalence and intensity of *T. trichiura* infection by cellophane thick smear and Stoll's egg counting techniques.

RESULTS

1. Short-term Efficacy of Mebendazole on *T. trichiura* Infection

Although the majority of the treated cases were of light worm burdens less than 1,000 in E.P.G. value, the short-term cure efficacy of meben dazole on *T. trichiura* infection was, in general, not so satisfactory (Table 1). When the drug was given less than 400 mg in total dose, the cure and egg reduction rates after 3 weeks were lower than 20 and 55% respectively. In 600 mg total dose groups, a little higher efficacy was obtained, however, the rates were in range from 43% to 67%. When the total dose increased to 800 mg in 4-day course regimen, 64.0 and 95.2% in cure and egg reduction rates were obtained, however, when 800mg was divided into 4 and given for 2 days, the efficacy was not so good as that. In case of the highest dose group (1,200 mg) in 6-day course regimen,

Table 1. The short-term efficacy of mebendazole in treatment of *T. trichiura* infection after 3 weeks

Total dose(Regimen) (mg)	No. treated	No. follow-up	No. cured	Cure rate(%)	Pre-treat. total EPG(mean)	Post-treat. total EPG	Egg reduct. rate (%)
100~300(single)	164	141	25	17.8	33,300(236)	25,100	24.6
400(100×2×2 days)	48	40	6	15.0	12,000(300)	5,400	55.0
600(single)	21	12	5	41.7	1,900(158)	1,300	31.6
600(300×1×2days)	88	51	22	43.1	11,830(232)	3,900	67.0
600(100×2×3days)	195	101	34	33.7	26,300(260)	8,650	67.1
800(200×2×2days)	36	26	10	38.5	2,500 (96)	600	76.0
800(100×2×4days)	33	25	16	64.0	4,200(168)	200	95.2
1,200(100×2×6days)	42	34	20	58.8	6,100(179)	400	93.4
Average	627	430	138	32.1	98,130(228)	45,550	53.6

Table 2. The results of follow-up examinations on 3 and 7 weeks after treatment

Total dose(Regimen) (mg)	No. follow-up	No. cases(%) who revealed			
		*——	−+	+−	++
600(300×1×2days)	32	5(15.6)	8(25.0)	1 (3.1)	18(56.3)
600(100×2×3days)	28	7(25.0)	5(17.9)	4(14.3)	12(42.9)
800(200×2×2days)	26	7(26.9)	3(11.5)	3(11.5)	13(50.0)
800(100×2×4days)	25	9(36.0)	7(28.0)	1 (4.0)	8(32.0)
1,200(100×2×6days)	34	18(52.9)	2 (5.9)	5(14.7)	9(26.5)

* ——: follow-up results after 3 and 7 weeks respectively

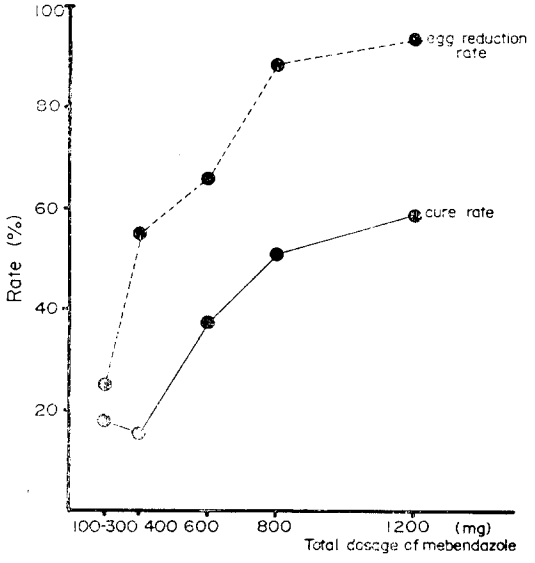

Fig. 2. Cure and egg reduction rates of mebendazole in treatment of *T. trichiura* infection according to total dosages used.

the efficacy, 58.8 and 93.4%, was not different from that obtained by 800 mg in 4-day course regimen.

Table 3. The pre-treatment result of stool examination in Siheung Gun for long-term observation of control efficacy by mebendazole

Kinds of helminths	No. egg posit. cases (%)
No. total subjected people	551
No. stool exam.	398
Overall helminth egg positive cases	210(52.8)
Trichuris trichiura	165(41.5)
Ascaris lumbricoides	54(13.6)
Taenia sp.	17 (4.3)
Pygidiopsis summa	9 (2.3)
Clonorchis sinensis	2 (0.5)
Hookworm	1 (0.3)

Another follow-up examination done on higher dose groups 7 weeks after treatment revealed a few cases of delayed cure ('+ −' in Table 2). However, there were still many egg positive cases apparently revealing treatment failure. Moreover, there were also some cases who were egg negative after 3 weeks but converted to egg positive after 7 weeks.

In summary of the results, it was shown that

Table 4. Results of follow-up stool examinations for prevalence of *T. trichiura* after blanket repeated mass chemotherapy

*Group	No. subjected people	May, 1982	August, 1982	November, 1982	February, 1983	May, 1983
		No.egg posit. / No.(%) exam.	No.egg posit. / No.(%) exam.	No.egg posit. / No.(%) exam.	No.egg posit. / No.(%) exam.	No.egg posit. / No.(%) exam.
I	92	24/60 (40.0)	15/41 (36.6)	15/39 (38.5)	9/28 (32.1)	7/15 (46.7)
II	265	95/229 (41.5)	33/124 (26.6)	26/112 (23.2)	25/112 (22.3)	14/72 (19.4)
II-1	95	34/85 (40.0)	9/43 (20.9)	6/36 (16.7)	5/36 (13.9)	1/18 (5.6)
II-2	170	61/144 (42.4)	24/81 (29.6)	20/76 (26.3)	20/76 (26.3)	13/54 (24.1)
III	112	30/71 (42.3)	— (—)	7/23 (30.4)	— (—)	12/36 (33.3)
IV	82	16/38 (42.1)	— (—)	— (—)	— (—)	2/10 (20.0)

* Group I : Placebo control(every 3 months)
Group II : Mebendazole 600mg (every 3 months)
Subgroup II-1; conventional 3-day course regimen
Subgroup II-2; single or two divided doses
Group III : Mebendazole 600mg in conventional regimen(every 6 months)
Group IV : Mebendazole 600mg in conventional regimen(every 12 months)

the higher the dose of mebendazole the better the efficacy(Fig. 2).

2. Long-term Trichuriasis Control Efficacy by Mebendazole

In this trial, a total of 600mg dose of mebendazole was applied in consideration not only of the cost-efficiency of the scheme but of the difficulty in field application of higher doses in 4-day or 6-day course regimen.

The pre-treatment status of helminthic infections was shown in Table 3. When the subjected village was divided into 4 groups, the egg positive rates of *T. trichiura* in each group were much similar to one another ranging from 40.0 to 42.3% (Table 4).

In placebo control group(Group I), the follow-up egg positive rates of the subjected inhabitants revealed a small fluctuation but the rates remained within the range, 32.1~46.7%.

Contrarily, other three groups(Groups II, III and IV) revealed a decreasing tendency in egg positive rates. In Group II, 3-month interval group, the egg positive rate one year after the first mass chemotherapy was 19.4% which was the lowest among the three interval groups. When the Groups II-1 and II-2 were compared, the control efficacy was far better (from 40.0 to 5.6%) in the former(conventional regimen) group (Table 4 and Fig. 3). There was only a slight decreasing tendency in Group III. The

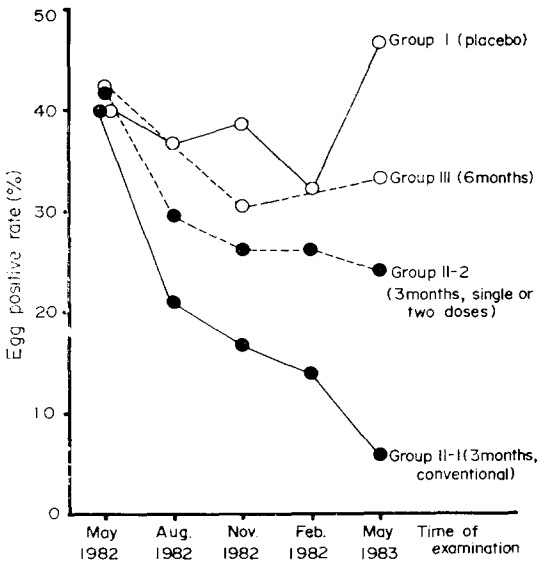

Fig. 3. Comparative control efficacy of mebendazole on prevalence of *T. trichiura* infection according to interval and drug regimen of mass treatment.

egg positive rate in Group IV was of lower value than expected, however, it was probably due to small number of follow-up cases.

The average pre-treatment E.P.G. value in each group was in the range, 92-327 (Fig. 4). By repeated mass chemotherapy, the value decreased especially in Groups II-1 and III.

Throughout the studies, long-term or short-term, no special adverse effects by mebendazole

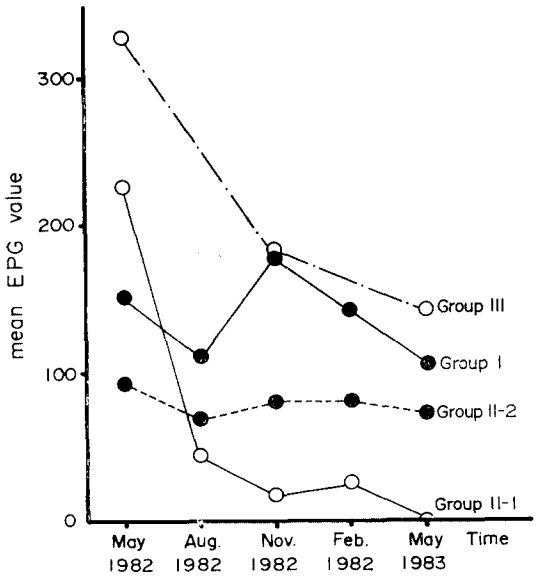

Fig. 4. Comparative efficacy of mebendazole on the intensity of *T. trichiura* infection according to interval and drug regimen of mass treatment.

treatment were encountered.

DISCUSSION

Mebendazole appeared not highly effective in individual treatment of *T. trichiura* infection in this study. The cure rate was a little higher by increased doses, 800 or 1,200 mg divided for 4 or 6 days, however, it was still not satisfactory.

The cause of failure by mebendazole in complete elimination of *T. trichiura* worms from human colon is not fully explained. Two factors have been postulated; share of smaller amount of drug per parasite in heavy burden or multiple parasite cases, and/or severe diarrhea which allows insufficient time and concentration of drug to have contact with worms (Wolfe *et* Wershing, 1974; Scragg *et* Proctor, 1977 & 1978; Kan, 1983). In this connection, Scragg *et* Proctor (1978) obtained 100 % cure rate by repeated 6-day course mebendazole treatments and additional use of loperamine, a potent antidiarrheal agent, to 25 heavy infection cases.

In the authors' opinion, however, it should also be considered that, mebendazole might not act on young *T. trichiura* worms, if then, new eggs would be produced from them after full maturation during the follow-up period. In this study, the worms of *T. trichiura* were collected (16 from 12 cases) from whole-day stools passed for 7 days after mebendazole treatment, and all of the collected worms were grossly fully mature ones. Furthermore, there was 6-30% of relapse ('− +' in Table 2) among the follow-up cases 7 weeks after treatment. It seems hardly possible that such cases were due to new infection, since the maturation period of this worm is known about 3 months(Seo, 1978). The similar concepts on the limitation of drug efficacy on young intestinal nematodes were mentioned for pyrantel pamoate on migrating *A. lumbricoides* (Cho, 1977; Seo *et* Chai, 1980) and for mebendazole, pyrantel, pyrvinium and piperazine on immature young *E. vermicularis* worms (Cho *et al.*, 1977; Hong *et al.*, 1979).

In spite of the poor efficacy of mebendazole in individual treatment, the drug appeared to be fairly effective in long-term control of trichuriasis in endemic areas. The best control efficacy was obtained from 3-month interval group especially by conventional regimen. This result may be explained in two ways.

Firstly, the so-called inhibitory effect of mebendazole on the development of *T. trichiura* eggs up to 7 days following initiation of the conventional treatment (Wagner *et* Pena Chavarria, 1974 a & b; Paul *et* Zaman, 1975; Iyngkaran *et al.*, 1976; Wagner *et* Rexinger, 1978) seems to have been an important factor in reducing the reinfection source and consequently in control. However, such effect may have partially participated in control, since many worms that resisted the treatment would, thereafter, have produced new viable eggs.

The second factor is the 3 months of the treatment interval, which correspond with the prepatent maturation period of *T. trichiura* in human. In 3-month interval scheme, the reinfected worms, if any, might have been eliminated before laying many eggs which, in turn, lead

to contamination of minimum amount of eggs at environment and facilitated the control. A success in eradication of *A. lumbricoides* infection applying 2-month interval (prepatent period of this worm) repeated mass chemotherapy with pyrantel pamoate was reported in a rural community (Seo *et* Chai, 1980).

From the aspect of feasibility of mebendazole in endemic fields, the treatment regimen, single or multiple, is very important. But in this study, the long-term control efficacy even in 3-month scheme was not so good when the drug was given in single or two divided doses (Group II-2 in Table 4 & Fig. 3). This result was difficult to explain, since the short-term cure efficacy was nearly the same as 3-day regimen in this study. A possible speculation can be that the egg reduction efficacy, about half of 3-day regimen group in this study, may have concerned. Furthermore, although there is no report, single or two doses of mebendazole may reveal much less degree of ovicidal activity than 6 divided doses in 3-day regimen.

SUMMARY

Mebendazole was tested for its efficacy in individual treatment and mass control of *Trichuris trichiura* infection in Korea.

The results were as follows:

1. The efficacy of mebendazole in 430 cases 3 weeks after treatment with mebendazole (100~1,200 mg) was not so satisfactory (15.0~64.0 and 24.6~95.2% in cure and egg reduction rates respectively). But it was observed that the higher the total dose of the drug the better the efficacy.

2. The egg positive rate of the inhabitants in mass control programme by 600 mg mebendazole decreased from 40.0 to 5.6% during one year, May 1982-May 1983, by repeated blanket mass chemotherapy every 3 months (in conventional regimen), while the decrease was less marked or unrecognizable in 3-month (single or two divided doses), 6-month, 12-month interval and placebo control groups.

From the results, it was concluded that, although mebendazole was not highly effective in individual treatment of *T. trichiura* infection, it was fairly useful in mass control, by repeated mass chemotherapy every 3 months.

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=국문초록=

편충증 치료 및 집단관리에 있어서 메벤다졸의 효과

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편충증의 개인치료와 집단관리에 있어서 메벤다졸의 유용성 및 효과를 측정하였다.

메벤다졸(100~1,200mg) 투약 3주후 430명에 있어서의 치료효과는 15.0~64.0% 및 24.6~95.2%의 치유율 및 충란감소율을 보여 대체로 만족스럽지 못한 결과이었으나 메벤다졸의 총 투여량이 높으면 높을수록 치유율 및 충란감소율도 높아지는 것이 관찰되었다.

일정간격 반복투여(600mg용량)에 의한 집단관리군 주민(4개군, 총 551명)의 편충란양성율은 3개월간격(3일 분복군) 투여군에서 가장 현저한 감소추세를 보여 관리시작후 1년만에 40.0%에서 5.6%로 저하되었고, 3개월 간격(단회 또는 2회 분복군), 6개월, 12개월군 및 대조군에서는 감소추세가 완만하거나 거의 관찰되지 않았다.

이상의 결과로 보아, 메벤다졸은 편충의 개인치료에는 그다지 우수한 결과를 나타내지 않았으나, 3개월간격으로 반복투여하면 집단관리에는 유효한 약제가 될 수 있을 것으로 생각되었다.