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Effect of Two-Month Interval Mass Chemotherapy on the Reinfection of *Ascaris lumbricoides* in Korea

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INTRODUCTION

The prevalence of *Ascaris lumbricoides* infection in Korea was reported to be 41 per cent of general population according to the Ministry of Health and Social Affairs and the Korea Association for Parasite Eradication (1976). The still high endemicity of this worm in our country, in spite of many control trials, is of course due to persistent reinfection. The rapidity of reinfection was also remarkable according to Seo *et al.* (1980 b) in rural villages of Korea. In this connection, the control policy of ascariasis afterwards should be those which actively tackle the problem of reinfection.

Environmental sanitation and public health education *etc.* are good measures for reinfection control, though these are time consuming ones. Mass chemotherapy is an alternative to those, and should be the most reliable method as present situation in Korea. This method prevents, when repeated with proper interval, the accumulation of reinfection, and lessens the worm burden per case. It was already reported that the production of fertilized eggs as the source of further reinfection, was apparently reduced according to the decrease of worm burden (Seo *et al.*, 1979).

If we want to stop the fertilized ova production, thus to minimize the reinfection source, the treatment interval and the total duration of programme are important. In this respect, two factors in *Ascaris* biology are the prerequisite informations; the prepatent period in human host, and the longevity of the infective eggs outide the host. The treatment interval should not exceed the prepatent period and the duration should be, theoretically, longer than the survival time of the already contaminated eggs at surroundings.

The prepatent period of *A. lumbricoides* in human host has been estimated about 60—70 days (Galvin, 1968; Morishita, 1973; Seo *et al.*, 1980 c). According to Seo *et al.* (1980 c), the sexually matured *Ascaris* worms were longer than 10.5 cm in male and 12.5cm in female. Interestingly, the size of female was well coincided with maximum criteria of *young worms* collected by Cho (1977) after 2-month interval mass chemotherapy with pyrantel pamoate. Therefore, 2-month schedule with pyrantel was considered appropriate for prevention of further egg production.

However, the longevity of infective eggs in environment was reported variable according to geographical conditions and situations; about 1 year (Asada, 1923), up to 4—5 years (Morishita, 1973) or even 10 years (Brudastov *et al.*,

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1971).

Anyway, based on the above information, we tried to make a small rural village in Korea free from reinfection and new egg production by repeated mass chemotherapy on the whole population, every 2 months with pyrantel pamoate, for a long period up to 3 years. Finally, we would like to know whether reinfection control could be attainable only by this method.

MATERIALS AND METHODS

1. Subjected population and treatment

Three rural hamlets (Group A, B and C) in Haengjung-1-Ri, Hyangnam Myon, Hwasung Gun, Kyunggi Do, Korea were subjected in this study. The purpose of grouping was twofold; to determine the minimum effective dose of pyrantel pamoate, and to observe the effect of treatment interruption on later reinfection. Inhabitants of each group were treated bimonthly with 2.5, 5.0 and 10.0 mg/kg of pyrantel pamoate respectively, from June 1977. The treatment was repeated 18 times until May, 1980 in Group A, while it was interrupted after

Table 1. The basic scheme of the study

Sequent. No. of treatment (date)	Group	Population	No. treated	No. of examined for	
				Eggs	Worms
1 (Jun. 14, 1977)	A	130	110	77	33*
	B	130	108	86	34*
	C	134	113	90	31*
2 (Aug. 17, 1977)	A	137	120	89	78
	B	133	116	94	72
	C	136	107	87	70
3 (Oct. 15, 1977)	A	149	125	85	57
	B	126	109	76	59
	C	135	101	85	53
4 (Dec. 18, 1977)	A	149	126	85	53
	B	131	112	77	57
	C	138	101	91	71
5 (Feb. 11, 1979)	A	140	125	97	67
	B	132	117	91	64
	C	133	102	72	52
6 (Apr. 18, 1978)	A	146	132	90	57
	B	128	110	80	61
	C	123	92	68	50
7 (Jun. 24, 1978)	A	146	132	90	57
	B	129	110	57	39
	C	120	88	49	46
8 (Aug. 21, 1978)	A	148	128	—	—
	B	129	112	—	—
	C	120	92	—	—
9 (Oct. 18, 1978)	A	148	128	—	—
	B	129	112	—	—
	C	120	92	—	—
10 (Dec. 19, 1978)	A	146	128	97	46
	B	129	115	86	48
	C	120	95	61	39
11 (Feb. 14, 1979)	A	140	120	89	58
	B	120	—	60	—
	C	110	—	47	—
12 (Apr. 14, 1979)	A	134	112	49	37
	B	120	—	48	—
	C	110	—	34	—
13 (Jun. 20, 1979)	A	134	108	63	50
	B	120	—	39	—
	C	105	—	44	—
14 (Aug. 28, 1979)	A	134	108	64	37
	B	120	—	39	—
	C	105	—	46	—
15 (Oct. 30, 1979)	A	126	102	66	52
	B	116	—	48	—
	C	105	—	41	—
16 (Dec. 27, 1979)	A	120	100	54	41
	B	119	—	60	—
	C	105	—	41	—
17 (Feb. 28, 1980)	A	120	88	46	29
	B	120	—	41	—
	C	105	—	38	—
18 (May 8, 1980)	A	116	72	45	28
	B	120	81	61	45
	C	105	69	46	31
Total		6,508	4,311	3,137	1,706

* The low number of examination was due to insufficient orientation of the inhabitants to the complete collection of whole-day stool.

10 times until December, 1978 in Group B and C (Table 1). The intervals between treatments were not exactly 60 days. There were some 5—10 days' delay during the course of study.

In every treatment trials, all of the inhabitants of whole age and either sex were subjected to treatment without preliminary check of positivity for eggs. As summarized in Table 1 and 2, however, not all of them could be treated. Pregnant women were excluded from treatment until confinement. And there were always some absentees and reluctant individuals to treatment. But the covered proportions in each treatment were always higher than three quarters of whole population. New immigrants were immediately registered and included in the next treatment (Table 2).

2. Methods of follow-up and evaluation

The whole-day stool specimens were collected for 2 days after each treatment from each case. The specimens collected were examined both for eggs and for expelled *A. lumbricoides*. Egg examination was done by cellophane thick smear method with the firstly passed stool from each case. Only one sample was examined each time.

In worm examination, the number of expelled worms per case was, of course, counted each time and the length and weight of individual worm were measured. The purpose of measuring worms was to discriminate young worms which were reinfected during the recent 2 months (Cho, 1977; Seo *et al.*, 1980c). And male worms under 10.5 cm and 0.40 gm and females under 12.5 cm and 0.53 gm were considered to be sexually immature young worms. The percentage of cases with young worm(s) in the population was calculated in each follow-up.

We believe that the young worm detection results should be the more reliable index for evaluation of the efficacy of 2-month model in reinfection control, rather than the egg or total worm positive rates. Because the true reinfection cases between treatments should show neither any eggs in stool nor any matured worms in worm collection.

In treatment interruption groups (B and C), the follow-up study was made by only egg detection method next to February 1979 (the 11th treatment) (Table 1; Fig. 1).

RESULTS

1. Attitude of the subjected inhabitant

Because Korean people are relatively well educated on the parasitic infections, the necessity of this study was readily accepted by the inhabitant in the project area. Therefore, they were very cooperative to the treatment and follow-up examination especially during the initial half of study period. However, as the study progressed 1 year and more, they became a little boring of or unwilling to collect whole-day stools rather than drug administration, as shown in Table 1. Especially during the main season of rice cultivation, June, August and October each year, stool collection for 2 days was really difficult. It was reason why we should delete two times of stool collection on August and October 1978 (Table 1; Fig. 1 and 2).

The high rate of cooperation in stool collection during the initial period may partly have been due to easy recognition of expelled *Ascaris* worm or worms within 2 days after treatment. However, in later stage, they lost interest in the treatment because almost no recognizable worms were found due to decreased cases with worm(s), especially large ones.

2. Dose and side effects of pyrantel

The pre-treatment egg positive rates were, as shown in Fig. 1, not so different each other in Groups A, B and C; 48.1, 45.3 and 37.8% respectively. Two months after the first treatment, egg positive rates were downed to 10.1, 4.3 and 2.3% respectively and afterwards, the

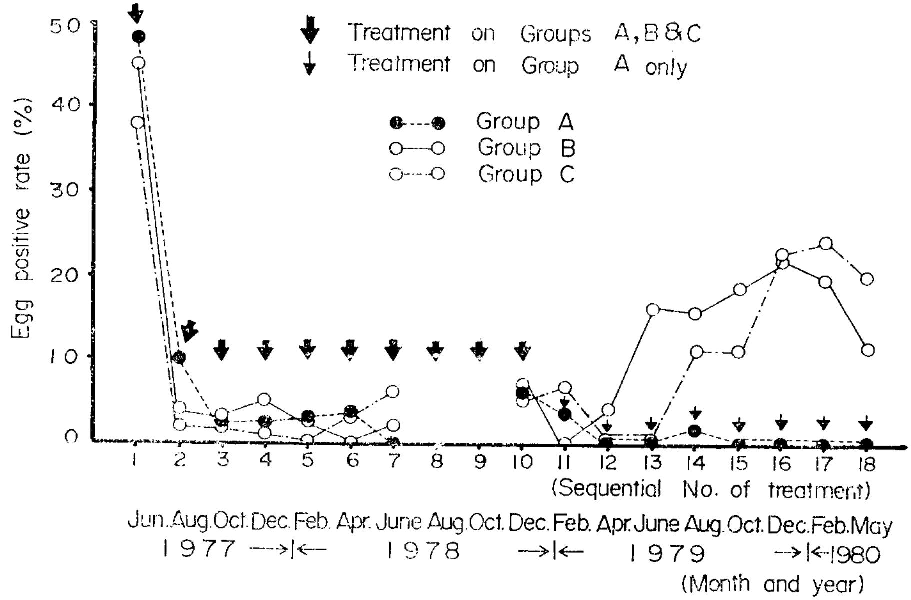

Fig. 1. The results of stool examination for *Ascaris* eggs by continuous 2-month interval mass chemotherapy.

rates remained lower than 6~7% until the 10th treatment on December 1978. No difference was observed in decreased positive rates among the three dosage groups. Accordingly, the quarter of the conventionally recommended dose of pyrantel pamoate was equally effective as the higher doses in case of repeated use during reinfection control of *A. lumbricoides.*

The drug was readily accepted by the people even those who were reluctant to follow-up stool collection. The inhabitants were instructed to tell the side effects by pyrantel treatment during the next 2 days of follow-up visits. Out of total 4,311 treatments during the whole period of study, only 8 cases actually complained of side effects. Those included abdominal pain and/or diarrhea once or more times. The incidence of side effects showed no difference between the dosage regimens and the frequency of drug administration.

3. Effect of 2-month interval treatment on subsequent reinfection

By means of worm collection technique, several egg negative but reinfected cases were detected in each treatment. They were, in most cases, infected with immature young worm(s).

Table 3 shows the number of worms collected after each treatment. In the first treatment trial,

Table 2. Summarized census data of study Groups

Groups	A	B	C
Population	116~149	120~133	105~138
No. of immigrants per 2 months (avg.)	0~14(2.2)	0~5(1.4)	0~15(2.9)
No. of emigrants per 2 months (avg.)	0~11(3.1)	0~7(1.4)	0~12(2.9)
No. of absentees per trial	10~22	12~20	10~25
No. of reluctant cases per trial*	0~9	5~12	3~8
Percentage of treated	73~90%	73~89%	73~84%

* Pregnant women were included.

Table 3. Result of worm collection throughout the study

Sequential No. of treatment	No. examined	No. of positive case	No. of collected worms			No. per infected	No. per population
			Mature	Immature young	Total		
1*	98	45	89	4	93	2.1	0.95
2*	220	14	25	9	34	2.4	0.15
3*	183	8	2	6	8	1.0	0.04
4*	181	21	11	14	25	1.2	0.14
5*	183	12	8	8	16	1.3	0.09
6*	168	5	1	4	5	1.0	0.03
7*	132	10	3	8	11	1.1	0.08
8*	—	—	—	—	—	—	—
9*	—	—	—	—	—	—	—
10*	133	9	14	2	16	1.8	0.12
11**	58	2	0	2	2	1.0	0.03
12**	37	1	0	1	1	1.0	0.03
13**	50	3	0	3	3	1.0	0.06
14**	37	1	2	0	2	2.0	0.05
15**	52	0	0	0	0	0.0	0.00
16**	41	0	0	0	0	0.0	0.00
17**	29	0	0	0	0	0.0	0.00
18**	28	0	0	0	0	0.0	0.00

* Data from Groups A, B & C **Data from Group A

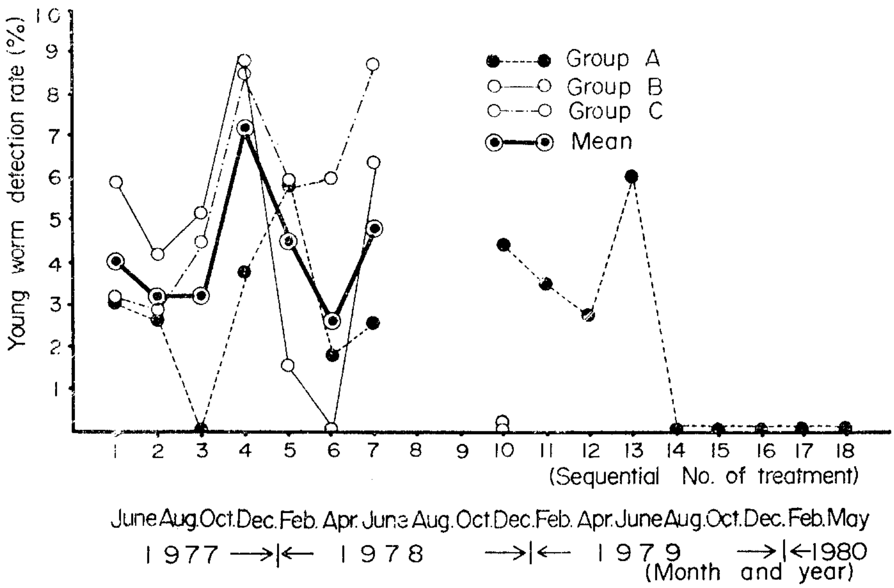

Fig. 2. Fluctuation of immature young worm detection rates in three Groups.

93 worms consisted of 89 mature and 4 immature worms were collected. But as the treatment was repeated; the number of collected worms decreased. Thus the indices, number of worms/infected case and number/population were also lowered.

The number of worms/infected case was 2.1-2.4 at initial 2 treatments, but decreased to around 1 thereafter until the 14th treatment. The number of worms/population was nearly 1.0 at the first treatment but decreased to 0.05 at the 14th treatment. The composition of the mature and immature worms was changed and the ratio reversed according to repetition of treatments (Table 3).

Fig. 2 shows the fluctuation pattern of young worm collection rates in three Groups, in which two apparent seasonal peaks were shown in the first year, *i.e.*, in summer(June) and in winter (December). After February 1979, treatment being continued only in Group A, the seasonal peaks were maintained until June, 1979(the 13th treatment). Thereafter, however, young worm was never detected during next 5 times of follow-up until the end of study.

4. Newly found infection cases during treatment

During the course of treatment in three Groups, there were 124 cases positive of egg and/or worm. They could be divided into three categories as presented in Table 4, *i.e.*, the true reinfection cases between treatments, the absentees (=drop-outs) in previous treatment and the infected immigrants. A total of 71 out of 124 were the true reinfection cases. The average number of such cases was about 3 per

Table 4. Number of the newly found infected cases in three Groups during the course of treatment

Category	No. of cases* in			Total
	Group A	Group B	Group C	
Infected immigrants	10	3	3	16
Absentees in previous treatments	14	13	10	37
True reinfection	24	21	26	71
Total	48	37	39	124

* Cases detected both by eggs and by worms

Table 5. Egg discharging patterns in newly found infected cases according to three category

Category	No. of cases	No. of cases with		
		False neg.	Unfert. egg	Fert. egg
Infected immigrants	16	2	6	8
Absentees	37	8	19	10
True reinfection	71	56*	13	2
Total	124	66	38	20

* False negative for eggs due to infection with immature young worms

trial in each group.

Epidemiologically, the unfertilized egg passers are of negligible importance and quite the same as the uninfected or false egg negative cases because they do not participate in spreading the infection. Thus, the egg discharging patterns in the above categories of positive cases were analyzed in Table 5. Among 124 newly found infected cases, 104 (83.9%) were either false egg negative or unfertilized egg passers. Out of remaining 20 fertilized egg passers 18 were either infected immigrants or absentees in the previous treatment.

5. Effect of treatment interruption

As already described, the drug treatment was interrupted in Group B and C after 10 times of bimonthly treatments. And afterwards stool examination for eggs was done until the end of this study. Within one year, the egg positive rate returned fairly high around 20%, which was about half of pre-treatment level(Fig. 1).

Because the egg positive rate represented only the cumulative incidence of the reinfection, the number of new egg passers during follow-up examination was calculated and compared with that of before interruption, as summarized in Table 6. The mean incidence of new egg passers per trial was 1.4~2.3 before interruption in three Groups. The rate decreased in Group A but were stationary or rather increased in Group B and C. The egg positive cases, at the

Table 6. Comparative incidence of new egg passers according to two stages of the study: Before and after treatment interruption

Sequent. No. of treatment	No. of follow-up	Group A*		Group B		Group C	
		No. of new egg passer	No. per trial	No. of new egg passer	No. per trial	No. of new egg passer	No. per trial
2~10(during treatments)	7	14	2.0	16	2.3	10	1.4
11~18(after interruption)	8	4	0.5**	27	3.4	19	2.4

* For comparison with Groups B & C. Chemotherapy was continued.
** New cases were found until Aug. 1979 (the 14th treatment)

Table 7. Proportion of the unfertilized egg passers to egg positive cases according to the stages of study in Groups B & C

Stages	Sequent. No. of treatment	No. of cases who passed			U/U+F*
		Unfert. eggs	Fertil. eggs	Total	
Pre-treatment	1	28	45	73	0.38
During treatments	2~10	65	27	92	0.71
After interruption	11~18	23	7	30	0.77

* U/U+F: Number of unfertilized egg passers/number of total egg positive cases

beginning of mass chemotherapy, were more likely of fertilized egg passers, however, the situation was reversed after treatments. The dominancy of unfertilized egg passers was maintained relatively well even after the interruption of treatment, as summarized in Table 7. This result suggests that, although the prevalence elevated fairly high after interruption, the fertilized egg production was still affected by the previous suppression of reinfection cycle.

DISCUSSION

In endemic areas of ascariasis, the reinfection phenomenon has been the most important obstacle during the control activity. According to Seo *et al.*(1980b), the prevalence rate at one year after mass chemotherapy was almost the same as the pre-treatment level and about half at 6th month, in some rural villages in Korea. Arfaa and Ghadirian(1977) also reported the rapid return of prevalence after single mass chemotherapy due to reinfection, and recommended 2-3 month interval continuous treatment in six rural communities in central Iran.

In order to control or eradicate *A. lumbricoides* infection, we adopted 2-month interval mass chemotherapy scheme. The intention of using 2-month scheme was, as already mentioned, to make the village free from further egg production. The duration of treatment intended was until the possible life span of already produced and contaminated eggs at surroundings, *i.e.*, several years. If the treatments were repeated under the above principle, the reserve of already contaminated eggs would be exhausted and then, the reinfection during the course of treatment would be a function of only the still surviving eggs in the community. The incidence of reinfection would decrease as much as the reserve reduced, and the final outcome expected was the stopping of reinfection process itself.

The result obtained in this study seemed not so different from expected. The principle of 2-month interval mass chemotherapy by pyrantel were appropriate lest the reinfected worms should grow until oviposition. Only 2 out of 71 true reinfection cases produced fertilized eggs and most of them (56 cases, 78.9%) harboured young worms, as shown in Table 5. Finally it could be said that the literal reinfection control was achieved after 28 months (on the 15th treatment) in Group A. The total duration needed may have been longer than this result because it was difficult to conclude that really not any reinfection had occurred during the last 5 times of follow-ups, reminding the far decreased number of examination cases for worms at those times.

Based on the exactly same principle as in this study, Biagi and Rodriguez (1960) undertook mass treatment with monthly administration of piperazine in a tropical village of Mexico. There, the reinfection was stated to have been controlled after 8 times of treatment. This rapid outcome in Mexico may have been due to far different situation in the reinfection incidence from Korea. The pre-treatment egg positive rate was 48.1% in this study and 28.3% in Mexico. The reason for the different interval, 1 month and 2 months, may be, in our opinion, that piperazine used by them could not remove the younger worms from intestine which would reach maturity within a shorter time than 2 months. In this connection, Fernando and Balasuriya (1977) in Ceylon failed to control ascariasis with piperazine probably because they used 2-month interval scheme with this drug.

When the mass chemotherapy was stopped after 20 months in Group B and C in this study, the egg positive rate returned fairly high within one year. This certainly means that reinfection still occurred and the reserve of infective eggs in the community was not entirely exhausted. In other words, the general life span of the infective eggs in surroundings may be longer than 20 months.

One social factor in this study should be pointed out here; the infected immigrants and the drop-outs at treatments. They probably played the role as new egg source during the course of study. But their epidemiological significance should not be exaggerated because of following reason. During one and half years, only 18 fertilized egg passers were introduced (Table 5) to about 400 population in three Groups, and they were treated in next trials.

Anyway, it should be mentioned that the success in reinfection control in Group A does not necessarily mean no more reinfection afterwards. The infective eggs would be introduced again from outside of the target village through migration of inhabitants after a period of time. Therefore, not so far as the study area is as wide as possible and the adjacent villages are included in the programme, it seems very difficult to keep a village free from further reinfection even after bimonthly mass chemotherapy for a long time.

The incidence of side effects by pyrantel pamoate was very low in this study. This drug is said highly safe and tolerable, however, such a low rate might be due to the attitude of local people. They were, in general, shy and would not like to tell every details of adverse effects due to drug administration to the favour-giving physicians. Therefore, the rate was supposed to be higher than that verbally complained.

The one thing we should have done was the examination of the eggs contaminated in soil. Recently many modifications of soil examination techniques were developed with good reproducibility. However, the results of examination may be variable according to the areas of sampling, conditions of soil, amount of examined sample *etc.* So, we did not select the soil examination as a follow-up indicator in the evaluation of the mass treatment efficacy.

SUMMARY

A trial to control reinfection cycle of *Ascaris*

lumbricoides was made in a rural village in Korea by blocking the process of new egg production. Chemotherapy with pyrantel pamoate was repeated bimonthly in three hamlet groups, each consisted of 105~149 inhabitants of whole age group. In one hamlet (2.5mg/kg dose) blanket mass treatment was repeated for 18 times from June 1977 to May 1980. In other two, 5.0mg and 10.0mg/kg dose groups, treatment was undertaken for 10 times from June 1977 until December 1978 and later reinfection pattern was observed.

Follow-up examination was made by whole-day stool collection for 2 days from each case after every treatment. The samples were examined both for eggs and worms, adult and immature young, of *A. lumbricoides.*

The results obtained are summarized as follows:

1. The pre-treatment egg positive rate in Group A, B and C was 48.1, 45.3 and 37.8% respectively.

2. The lowest dose of pyrantel pamoate, 2.5 mg/kg was equally effective as higher doses in case of repeated use for reinfection control.

3. Among 4,311 pyrantel treatments, only 8 cases complained of side effects such as abdominal pain and diarrhea.

4. When the blanket mass chemotherapy was continued 18 times in Group A, all of the examined inhabitants were free from reinfection and egg production from 28th month (the 15th treatment) until the end of study period, for 8 months.

5. When the mass chemotherapy was stopped after 10 times, the egg positive rate returned gradually up to half of pre-treatment level within one year.

6. From the analysis of total 124 positive cases during the course of follow-up, it was revealed that the mass chemotherapy with 2-month interval was successful for the suppression of fertilized egg production. However, social factors such as infected immigrants or absentees were inevitably encountered and involved in the fertilized egg production.

Summarizing the results, at least 28-30 months were needed to eradicate *A. lumbricoides* in the subjected area of Korea, by repeated blanket mass treatment bimonthly with a quarter dose of pyrantel pamoate. Furthermore, to lessen the social factors as a source of later reinfection, the project area of control programme should be extended as wide as possible.

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=國文抄錄=

二個月간격 연속 집단치료가 회충재감염에 미치는 영향

서울대학교 의과대학 기생충학교실 및 풍토병연구소
徐 丙 卨·蔡 鍾 一

어떤 지역에서 모든 주민에 대하여 2개월간격으로 pyrantel을 사용하여 연속 집단치료를 실시한다면 그 지역에서는 회충 수정란의 새로운 산출은 미연에 방지될 수 있다. 그런 경우 그 지역 주민의 회충재감염양은 이미 과거부터 축적되어 온 汚染충란중 살아있는 감염형 충란량의 함수 관계에 있다. 따라서 살아있는 감염형 충란의 농도가 사람 재감염을 일으킬 한계 이하로 떨어진다면 이론상 그 지역의 회충재감염은 완전히 단절된다.

이 연구에서는 실제로 회충재감염의 사슬이 계속 이어지고 있는 농촌지역에서 위의 방법으로 회충재감염 사슬을 끊을 수 있는지, 있다면 기간은 얼마나 걸리는가를 알아보고자 하여 실시하였다.

京畿道 華城郡 鄕南面의 3개 부락(이 연구에서는 A群, B群 및 C群)의 주민 105~149명에 대하여 A群의 경우 pyrantel pamoate 2.5mg/kg의 용량으로 1977년 6월부터 1980년 5월까지 모두 18회에 걸쳐 반복투약하여 재감염이 관리되는지를 알고자 하였다. 나머지 2개群들은 각각 5mg/kg및 10mg/kg의 용량으로 1977년 6월부터 1978년 12월까지 10회만 투약한 다음 중지하고 재감염이 어떤 양상을 띄는가를 관찰하였다.

투약후에 배출되는 2일간의 모든 大便을 모아 충란 및 충체검사를 실시하였다. 수집충체는 그 무게 및 길이를 측정하여 成蟲과 어린회충(young worm)으로 분류하여 어린회충의 감염까지 없을 때를 재감염이 끊어지는 것으로 판정하였다.

이 연구의 결과를 요약하면 다음과 같다.

1. 투약전의 회충충란 양성율은 群別로 각각 48.1%, 45.3% 및 37.8%이었다.

2. A, B 및 C群사이에 10회 추적검사성적에 차이가 없는 것으로서 pyrantel pamoate는 2.5mg/kg용량으로도 회충재감염관리를 위한 반복 집단치료에 유효한 것임을 확인하였다.

3. 모두 4,311명의 pyrantel투여중 약제에 의해 가벼운 복통이나 설사를 호소하는 경우가 8례 있었다.

4. A群에 있어서 모두 18회 계속된 투약의 결과 첫 투약후 28개월째부터 마지막까지 8개월간 검사자 모두에서 충란과 어린회충이 나타나지 않았다.

5. 투약을 중단한 B, C群에서는 중지후 1년동안에 충란양성율이 투약전의 약 1/2정도까지 올라가 재감염을 완전관리하는데 10회의 치료만으로는 성공할 수 없었다.

6. 追跡검사도중 양성자로 판명된 124명의 충란산출 양상을 분석해 보면, 2개월 간격의 집단치료는 수정란 산출을 성공적으로 억제하는 것으로 나타났다. 그러나 감염된 移住者나 集團投藥때 누락되었던 사람에서는 수정란 배출자가 일부 관찰되었다.

위의 결과를 종합하면 대상지역에 있어서 회충의 재감염을 완전히 방지하기 위해서는 2개월간격 집단치료법으로 적어도 28개월이상 계속해야 하는 것으로 나타났다. 또 이런 재감염 관리상태를 보다 완전하게 오랫동안 유지하고 인접지역등지로부터의 새로운 감염자의 移住를 막으려면 대상지역을 넓히는 것이 바람직하다고 생각되었다.