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Clinical Trial of Oxantel Pamoate (CP-14,445) on *Trichocephalus trichiurus* Infection

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INTRODUCTION

The whipworm, *Trichocephalus trichiurus*, is a common intestinal parasite of man throughout the world particularly in the subtropics and tropics. In Korea, actually, this infection remains a common problem of personal and public health. According to the results of recently conducted survey of helminthic infections (Seo et al., 1969), the whipworm infection was still found to be the most prevalent helminthiasis in this country. The prevalence rate of *Trichocephalus* infection, through the examination of 40,581 stool specimens collected from nationwidely, was 74.5%.

In spite of its vast occurrence and wide distribution, asymptomatic light or moderate infections were left untreated because of the absence of effective chemotherapeutics against *T. trichiurus* infection. Some drugs, such as hexylresorcinol, stilbazium iodide and dithiazanine iodide, have been used for symptomatic or asymptomatic infections; but their low efficacies, high toxicities and side reactions hindered the effective treatment of this helminthiasis. Recently, Howes (1972) reported that Oxantel (CP-14,445), a new anthelmintic, was proved to have high antiwhipworm activity in animals. Park et al. (1973) & Lim (1974) have also confirmed its high activity and low side effects against *T. trichiurus* infection in man.

The present study was undertaken to determine the efficacy of a single dose of Oxantel in the treatment of *T. trichiurus* infection and severity of the side effects in the doses used.

MATERIALS AND METHODS

Drug: Sample of a new anthelmintic, Oxantel (CP-14,445) oral suspension, was obtained from Pfizer Korea, Ltd. The chemical name of this antiwhipworm agent, a pyrimidine derivative, is trans-1, 4, 5, 6-tetrahydro-2-(3-hydroxystyryl)-1-methyl pyrimidine pamoate.

Case Selection: A total of 1,536 fecal speci-

The results of the this study were read at the 3rd International Congress of Parasitology, Munich, 1974, Spring meeting of Korean Society for Parasitology, 1974 and the 16th Annual Meeting of Korean Society for Parasitology, 1974.

mens from the urban and rural areas were examined, and 986 egg positive cases for *T. trichiurus* were detected (Table 1). Among these positive cases, 182 cases were selected for the anthelmintic trial. They were classified into 4 groups and were then subjected to anthelmintic treatment with different doses.

Table 1. Prevalence of *Trichocephalus trichiurus* infection in various groups

Group	Total No. of exam.	No. of positives	Prevalence (%)
Hwa-Gae Primary School	324	198	61.1
Gak-Shim Institute(A)	126	122	96.8
Dobong Orphanage	66	60	90.9
Seong-Shin Orphanage	78	27	34.6
Yong-In Mental Hospital	204	87	42.7
Shin-Heung High School	615	428	69.6
Gak-Shim Institute(B)	123	64	52.0
Total	1,536	986	64.2

Dosage Schedule and Administration: For the evaluation of anthelmintic effect of the Oxantel against *T. trichiurus*, 182 subjects were administered with a single dose of this oral suspension. As shown in Table 2, the given doses for each treated group varied from 10mg/kg to 25mg/kg body weight. The patients were requested neither the restriction of meals nor purgation.

Tabl 2. Classification and doses of antiwhipworm treatment with Oxantel pamoate (CP-1445)

Group	Subject	Dose
I	Hwa-Gae Primary School Children Gak-Shim Institute (A) Children Dobong Orphanage Children, Seong-Shin Orphanage Children	10mg/kg body weight, single dose
II	Gak-Shim Institute (A) Children Dobong Orphanage Children, Yong-In Mental Hospital Patients	15mg/kg, ibid.
III	Shin-Heung High School Students	20mg/kg, ibid.
IV	Gak-Shim Institute (B) Children	25mg/kg, ibid.

Evaluation: The negative conversion rate of egg out-put after treatment was ascertained by the cellophane thick smear method and Stoll's egg counting technique, and egg reduction rate was also determined by counting the number of eggs per gram of feces(EPG) before and after the treatment. The follow-up examination after the treatment was carried out on the 22nd day of post-treatment.

To determine and to record the incidence, type and severity of side effects, all the treated cases were examined for routine hematology, biochemical tests of liver function and urinalysis before and 10 days after the treatment.

RESULTS

Prevalence: The prevalence rate of *T. trichiurus* infection in this trial was summarized in Table 1. Of 1,536 fecal specimens, 986 cases were infected with *T. trichiurus;* thus the overall prevalence rate was 64.2%. Among the examined groups, children from Gak-Shim Institute(special institute for mental retarded children) showed the highest prevalence of 96.8%, and children from Seong-Shin orphanage which located in suburb of Seoul showed prevalence of 34.6%, the lowest.

Efficacy Evaluation: The anthelminitic efficacy of Oxantel was analysed on the bases of the negative conversion rate (cure rate) and and egg reduction rate.

1) Negative conversion rate (Cure rate)

The findings of the egg negative conversion in various treated groups were summarized in Table 3. Of 122 subjects with *T. trichiurus* given a single dose of 10mg/kg of Oxantel (Group I), 69 were converted egg negative. Although the rates were not uniform in subgroups, the average of cure rate of this group rated 56.6%. The Group II (15mg/kg) showed the rate of 87.9% while those rates of Group

Table 3. Egg negative conversion rates of *T. trichiurus* on egg counting at the 22nd post-treatment day by Oxantel treatment

Group (dose)	Subject	No. of treated	No. of negatives	NCR* (%)
Ⅰ (10mg/kg)	Hwa-Gae Primary School	19	6	31.6
	Gak-Shim Institute (A)	76	49	64.5
	Dobong Orphanage	6	6	100.0
	Seong-Shin Orphanage	21	8	38.1
	Subtotal	122	69	56.6
Ⅱ (15mg/kg)	Gak-Shim Institute (A)	11	8	72.7
	Dobong Orphanage	10	9	90.0
	Yong-In Mental Hospital	12	12	100.0
	Subtotal	33	29	87.9
Ⅲ (20mg/kg)	Shin-Heung High School	15	14	93.3
Ⅳ (25mg/kg)	Gak-Shim Institute (B)	12	9	75.0
	Total	182	121	66.5

*NCR: Negative Conversion Rate

Table 4. Egg reduction rates of *T. trichiurus* at the 22nd post-treatment day by Oxantel treatment

Group	Subject	Before treatment			After treatment			ERR* (%)
		No. of cases	Total E.P.G.	Mean E.P.G.	No. of posit.	Total E.P.G.	Mean E.P.G.	
Ⅰ	Hwa-Gae	19	21,000	1,105	13	5,000	385	76.2
	Gak-Shim(A)	76	154,000	2,026	27	14,300	530	90.7
	Dobong	6	8,900	1,483	0	0	0	100.0
	Seong-Shin	21	44,700	2,129	13	4,800	369	89.3
	Subtotal	122	228,600	1,874	53	24,100	455	89.5
Ⅱ	Gak-Shim(A)	11	10,600	964	3	3,300	1,100	68.9
	Dobong	10	19,000	1,900	1	200	200	99.0
	Yong-In	12	5,300	442	0	0	0	100.0
	Subtotal	33	34,900	1,058	4	3,500	875	90.0
Ⅲ	Shin-Heung	15	13,100	873	1	0	0	100.0
Ⅳ	Gak-Shim	12	14,300	1,192	3	600	200	95.8
	Total	182	290,900	1,598	61	28,200	462	90.3

Ⅲ (20mg/kg) and Group Ⅳ (25mg/kg) appeared 93.3% and 75.0% respectively. Among 182 cases, the total number of treated in this trial, 121 turned to egg negative; thus the overall cure rate was 66.5%.

2) Egg Reduction Rate

Table 4 shows the total egg counts of various groups before and after the treatment and the egg reduction rates after the treatment. Among the treated groups, Group Ⅲ (20mg/kg) showed the highest rate and the lowest was observed in Group Ⅰ (10mg/kg). In this single dose of

Oxantel treatment trial, all the groups revealed relatively good efficacy of anthelmintic treatment by showing the overall egg reduction rate of 90.3%. The mean EPG of all 4 groups fell from the level of 1,598 to 462.

Table 5 gives the distribution of cases by grades of worm burden (EPG) before and after the treatment. From this Table, it is apparent that most of positive cases were moved to the range of lower EPG grades 22 days after the treatment, in comparison with the initial distribution of cases.

Side Reactions: Side effects were recorded in only a few cases but these were so mild in almost all instances and nearly always confined to transient nausea and vomiting that none required specific treatment for side effects. The drug was well tolerated and its acceptability was excellent.

Complete blood cell counts and serum biochemistry were performed for all treated cases. Serum biochemistry considered of bilirubin, alkaline phosphatase, GOT and GPT and blood urea. Microscopy of urine and routine testing for protein and glucose were also carried out. No significant changes in these tests were monitored before and after treatment.

A few cases showed abnormalities in these tests prior to treat because of co-existing disease such as hepatitis, etc.; these findings were not aggravated by the administration of this drug.

Expelled Worms: As a reference, a parasitological observation was undertaken for the expelled worms. They were collected from all the cases treated by filtering stool specimens passed on lst, 2nd and 3rd post-treatment day. As shown in Table 6, a total of 1,244 worms were collected, and 45.0% of those worms were found expelled on lst post-treatment day. Rest of them were expelled on 2nd day(40.7%) and 3rd day (14.3%). From the observation of these worms, it was learned that their sex ratio was 1.03 : 1. Actually male and female worms expelled were 630 and 614 respectively, almost

Table 5. Distribution of *T. trichiurus* egg counts by grades before and 22 days after the Oxantel treatment

Group	Subject	Before treatment				After treatment			
		Grade Ⅰ	Grade Ⅱ	Grade Ⅲ	Total	Grade Ⅰ	Grade Ⅱ	Grade Ⅲ	Total
Ⅰ	Hwa-Gae	14	4	1	19	13	0	0	13
	Gak-Shim(A)	26	48	2	76	21	6	0	27
	Dobong	2	4	0	6	0	0	0	0
	Seong-Shin	8	12	1	21	11	2	0	13
	Subtotal	50	68	4	122	45	8	0	53
	(%)	(41.0)	(55.7)	(3.3)	(100)	(84.9)	(15.1)	(0)	(100)
Ⅱ	Gak-Shim(A)	8	3	0	11	2	1	0	3
	Dobong	1	9	0	10	1	0	0	1
	Yong-In	12	0	0	12	0	0	0	0
	Subtotal	21	12	0	33	3	1	0	4
	(%)	(63.6)	(36.4)	(0)	(100)	(75.0)	(25.0)	(0)	(100)
Ⅲ	Shin-Heung	11	4	0	15	1	0	0	1
	(%)	(73.3)	(26.7)	(0)	(100)	(100)	(0)	(0)	(100)
Ⅳ	Gak-Shim(B)	4	8	0	12	3	0	0	3
	(%)	(33.3)	(66.7)	(0)	(100)	(100)	(0)	(0)	(100)
	Total	86	92	4	182	52	9	0	61
	(%)	(47.3)	(50.5)	(2.2)	(100)	(85.2)	(14.8)	(0)	(100)

Grade Ⅰ : EPG 100-999, Grade Ⅱ : EPG 1,000-4,999, Grade Ⅲ : EPG 5,000 or more

Table 6. Expelled worms after the Oxantel treatment

Group	Subject	Worms collected									Subtotal		Total	Sex ratio M : F	Worms per capita
		D+1			D+2			D+3							
		M	F	T	M	F	T	M	F	T	M	F			
I	Hwa-Gae	43	26	69	21	8	29	0	0	0	64	34	98	1.88 : 1	5.2
	Gak-Shim (A)	15	27	42	20	28	48	2	2	4	37	57	94	0.65 : 1	15.7
	Dobong	28	28	56	12	14	26	12	17	29	52	59	111	0.88 : 1	18.5
	Seong-Shin	67	61	128	97	103	200	37	44	81	201	208	409	0.97 : 1	19.5
	Subtotal (%)	153	142	295 (41.4)	150	153	303 (42.6)	51	63	114 (16.0)	354	358	712 (100)	0.99 : 1	13.7
II	Gak-Shin(A)	32	36	68	38	33	71	6	9	15	76	78	154	0.97 : 1	14.0
	Dobong	60	54	114	46	45	91	8	2	10	114	101	215	1.13 : 1	21.5
	Yong-In	7	10	17	4	2	6	3	1	4	14	13	27	1.08 : 1	2.3
	Subtotal (%)	99	100	199 (50.3)	88	80	168 (42.4)	17	12	29 (7.3)	204	192	396 (100)	1.06 : 1	12.0
III	Shin-Heung (%)	14	16	30 (37.0)	13	10	23 (28.4)	15	13	28 (34.6)	42	39	81 (100)	1.08 : 1	5.4
IV	Gak-Shim(B) (%)	18	18	36 (65.5)	10	2	12 (21.8)	2	5	7 (12.7)	30	25	55 (100)	1.20 : 1	4.6
	Total (%)	284	276	560 (45.0)	261	245	506 (40.7)	85	93	178 (14.3)	630	614	1,244 (100)	1.03 : 1	11.1

D+1 : 1 day after the treatment
D+2 : 2 days after the treatment
D+3 : 3 days after the treatment
M : Male whipworm
F : Female whipworm
T : Total number of male and female

the same in number. By calculating with these expelled worms in stool specimens, worm burden per capita was 11.1.

DISCUSSION

Until recently no safe or effective chemotherapeutic agents have been available. The usual oral anthelmintics do not reach the cecal site of infection in sufficient quantities to remove most of the deeply embedded whipworms.

Though hexylresorcinol has been used in removing the worms by oral administration or enemas, but result was not so satisfactory whereas side effects were severe(Jung and Beaver, 1952; Faust et al., 1968). A newer cyanine dye, stilbazium iodide (Monopar) appears to be much better tolerated by the patient (Huang and Brown, 1964), but its cure rate is about 40%. Dithiazanine iodide(Abminthic or Delves) also a cyanine dye, was effective but too toxic to cause fatal side effects and has been withdrawn from the market. Thiabendazole, not satisfactorily effective in a short course, was only effective when given over a course of 11 to 30 days (Whalen et al., 1969). Bephenium hydroxynaphthoate(Alcopar), Pyrvinium pamoate(Povan) have shown only moderate effectiveness against *T. trichiurus* infection.

So it is always needed to apply these remedies with higher dosages or longer courses and it is difficult to eradicate whipworms in mass treatment. In this connection, the most effective and convenient anthelmintics against *T. trichiurus* infections are urgently demanded.

Recent years, the high efficacy of Oxantel, a new drug, has been reported in the treatment of *Trichocephalus* infections (Howes, 1972; Park et al., 1973; and Bhaibulaya et al., 1973; Lim, 1974).

Rim et al. (1974) conducted the clinical trial of Oxantel and obtained 57.1% of cure rate in 10mg/kg of Oxantel treated group and 94.1% in 15mg/kg treated group respectively. The findings in present study confirm the high activity of Oxantel when given in a single dose and its good toleration and safety. The present authors obtained a cure rate of 66.5% and egg reduction rate of 90.3% in the series of trials with a single dose of 10 to 25 mg/kg of Oxantel. Among the different dosages, the best result (93.3% of cure rate and 100% of egg reduction rate) was obtained in the Group Ⅲ (20mg/kg).

By considering the average worm burden (EPG 649) of Korean populations (Seo et al., 1969), it is recommended that a single dose of 15mg/kg or 20mg/kg of Oxantel is administered to treat *Trichocephalus* infected case in safe and good tolerance.

SUMMARY

The present clinical trial was conducted to determine the efficacy and tolerance of Oxantel (CP-14,445), one of pyrimidine derivative, in the treatment of *Trichocephalus trichiurus* infection 182 cases who harboured *T. trichiurus* were treated with Oxantel in a single dose of 10 to 25 mg/kg of body weight. For the evaluation, the negative conversion rate and egg reduction rate were calculated before and 22 days after the treatment.

The results obtained were as follows:

1. The prevalence rate of *T. trichiurus* infection in present study was 64.2% by examining 1,536 fecal specimens collected.
2. The overall negative conversion rate was 66.5%, while the highest rate (93.3%) was obtained in the group treated with 20mg/kg of Oxantel (Group Ⅲ). The lowest rate(56.6%) was observed in Group I (10mg/kg).
3. The overall egg reduction rate on present study was 90.3%. The highest rate, 100% of egg reduction was also obtained in Group III (20mg/kg).
4. From the observation of 1,244 expelled worms, it was known that 45.0% of collected worms were expelled on the first of post-treatment day, and male and female worms were about the same in number(1.03 : 1). Average worm burden per capita was 11.1 in this observation.
5. The medication was readily accepted and tolerated by all the treated cases. On the hemograms, urinalysis and liver function tests, no significant differences were noted before and after the drug administration. Side reactions were so mild and transient that none required specific treatment.

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=국문초록=

Oxantel pamoate에 의한 鞭蟲症의 治療效果

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우리나라에 蔓延하고 있는 鞭蟲症의 發生頻度, 感染强度 및 그 治療藥을 調査코저 1,536名의 大便檢査를 實施하고 986名의 鞭蟲卵 陽性者를 索出하여 그 中 182名에 대해서 새로운 鞭蟲藥인 Oxantel(CP-14,445)를 10-25mg/kg用量으로 投藥, 그 驅蟲效果를 檢討하였다.

1. 本 調査에서 鞭蟲發現率은 64.2%였으며 治療對象者 182名의 平均 E.P.G.는 1,598이었다.
2. 平均 蟲卵陰轉率(治癒率)은 66.5%였으며 治療群中 20mg/kg投與群에서 가장 높은 陰轉率 (93.3%)을 보였고, 10mg/kg投與群에서 가장 낮았다.(56.6%)
3. 平均 蟲卵減少率은 90.3%였으며 역시 20mg/kg投與群에서 가장 減少率이 높았으며(100%), 10mg/kg投與群에서 가장 낮았다.(89.5%)
4. 排出蟲體를 수집, 觀察한 결과 投藥後 第1日에 總 1,244마리中 45.0%, 第2日에 40.7%가 排出됨을 알았고 그 雌雄比는 1 : 1.03이었으며 平均 排出蟲體數는 1人當 11.1마리이었다.
5. 投藥前後에 施行한 血液, 尿 및 肝機能檢査에서 特異所見이 發見되지 않았으며 極小例에서 一過性이고 輕微한 副作用이 나타났으나 治療를 要하지는 않았다.