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Anthelmintic effect of Amidantel (Bay d 8815) against *Ancylostoma duodenale* infection

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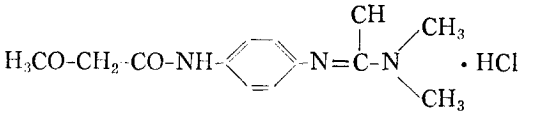
INTRODUCTION

Many drugs are available for the treatment of hookworm infections. Among them, tetrachlorethylene, bephenium hydroxynaphthoate, pyrantel pamoate and mebendazole etc. are safe and effective drugs in hookworm infections. The ideal drug for hookworm must be effective against both *Ancylostoma duodenale* and *Necator americanus* with a small single dose and must not produce intolerable side effects. Recently pyrantel pamoate has become the drug of choice for both hookworm infections; 10 mg/kg bwt (=body weight) orally once a day for 3 consecutive days for *Necator* and 1 day for *Ancylostoma* without any serious side effect (Rim *et al.*, 1973).

A recently developed new compound, Amidantel (Bay d 8815) has been expected as a highly effective drug against *Ascaris lumbricoides*, *A. duodenale*, *N. americanus* and *Strongyloides stercoralis*, as the results of the animal experiments on the anthelmintic activity (Wollweber *et al.*, 1979). Amidantel is a white crystalline powder and a new aminophenylamidine with an interesting anthelmintic spectrum. It is used in form of a hydrochloride which is very easily soluble in water and ethanol, practically insoluble in acetone and acetic ester. The chemical name and structural formula of the compound are the following: N-4-1-(Dimethylamino) ethylidene -amino-phenyl-2-methoxyacetamide hydrochloride (Amidantel, Bay d 8815)



The present study is a first clinical evaluation of amidantel (Bay d 8815) in the treatment of *A. duodenale* infection. The purpose of this study is to determine the efficacy at a single dose of various dosages and to assess the tolerability in which the incidence, type and severity of the side effects in the doses used were observed.

MATERIALS AND METHODS

Two clinical trials were made to determine either the dose finding and dose confirming in use of amidantel against *Ancylostoma duodenale* infections.

The first trial was aimed primarily at finding out the drug tolerance of increasing dosages in patients of the trial area and secondarily, in investigating its efficacy in eliminating *Ancylostoma duodenale*, *Ascaris lumbricoides* and other

parasites. A single blind placebo-controlled study was carried out on 64 patients ranging in age from 12 to 59 years infected with *A. duodenale* with or without combinations of *A. lumbricoides*, *Trichuris trichiura* and *N. americanus etc.* The following four dosage schemes were applied in each 16 cases and the drug was given after a main meal.

a) 1×3.0 mg/kg body weight (=bwt)
b) 1×6.0 mg/kg bwt
c) 1×9.0 ~10.0 mg/kg bwt
d) Placebo (The dosage for patients to be given placebo was the same as calculated for patients with corresponding body weight receiving dosis (c))

The second trial was designed to confirm the findings of the toleration and efficacy of amidantel using the dosis which proved most effective in the first trial. Seventy-six patients ranging in age from 14 to 69 years were given either a single dose of 8.0 mg/kg bwt (32 cases), 6.0 mg/kg bwt (31 cases) or 5.0 mg/kg bwt (13 cases) of amidantel. The efficacy was also evaluated in this trial including patients who are infected by one or both hookworm species as well as other intestinal helminths frequent in the trial areas.

In parasitological examinations for hookworm prior to treatment, identification of hookworm species according to the method of Harada and Mori (1955) or its modification after Sasa was made twice, and in each time 30 larvae were examined. One stool per day was examined by Stoll's egg counting method on 3 consecutive days. Of each stool 4 replicates of the same weight were examined. Shortly after medication, worm counting was carried out with 3 consecutive stools. Each stool was filtered and washed. The worms thus obtained were identified and determined regarding sex.

Follow-up examinations and assessment of efficacy

The follow-up examinations and assessment of efficacy were carried out in the following 2 steps.

Step 1: During the 3 consecutive days from 14th to 16th day after treatment, one stool was collected on each day and egg counts were made in 4 replicates of each stool using the method of Stoll. If eggs were not found in all aliquots, examination for eggs were made in the same stool samples but using Formalin-ether concentration method (Ritchie, 1948). In case eggs could not be detected again, patient will proceed to Step 2. In case any eggs were found in all aliquots, follow-up was terminated, and assessment was classified as *failure*. If eggs were found in only half of these aliquots, *i. e.* up to 6 aliquots, the negative aliquots only were examined by means of the concentration method to determine the degree of egg reduction. The assessment was classified as *poor* therapeutical efficacy. The efficacy was calculated on the rate of egg reduction obtained in comparison to mean egg output prior to therapy, and a coproculture was made for identification of the species.

Step 2: During the days from 28th to 30th day after treatment the same procedure as Step 1 repeated examining 3 stool, *i.e.*, 4 aliquots of each stool after Stoll. If all 12 replicates were negative again, examination for eggs was repeated using a concentration method.

In case egg was not detected in any of the aliquots, patient was cured parasitologically. The assessment was classified as *excellent* therapeutical efficacy. In case eggs were found in some aliquots examined after Stoll, percentage of egg reduction was calculated with regard to mean egg output prior to therapy. The assessment was classified as *fair* therapeutical efficacy. If eggs were only found in some aliquots examined by concentration method, assessment was classified as *good* therapeutical efficacy. In these occasions, a coproculture was also made for identification of the species.

In the other concomitant helminthic infections, the parasites were differentiated according to species and the degree of infection was determined for each parasites on the basis of egg count. For assessing drug efficacy the same criteria were applied as for the evaluation of hookworm infection.

In clinical examination prior to treatment, the following laboratory examinations were carried out for blood picture including erythrocyte count, leucocyte count, platelet count, hematocrit, white cell differentiation, hemoglobin, erythrocyte sedimentation rate, mean corpuscular hemoglobin concentration; for liver function including testing of SGOT, SGPT, alkaline phosphatase, indirect and total bilirubin; for blood biochemistry including testing of total protein, albumin, cholesterol, cholesterol ester, fasting blood sugar; for renal function including testing of BUN, creatinine and urine analysis. For the physical examinations heart and circulatory function including blood pressure, pulse rate and ECG and nervous system including testing of function of cranial nerve, equilibrium, coordination power, rigidity, tonus, sensitivity of skin reflexes were observed. All objective and subjective symptoms existing before treatment which impair well-being were recorded. At the first day after medication, all the patients were carefully observed to ascertain the type and severity of side effects. Physical examinations were also applied on the first, on the days of 14th to 16th and the days of 28th to 30th day after treatment. At the end of follow-up period a final examination was made to assess the condition of the patient's general health after therapy.

RESULTS

1. The first trial (Dose finding)

A total of 64 patients infected with *Ancylostoma duodenale* were treated with amidantel (Bay d 8815) in the form of tablet (125 mg of each) in a single dose of 3.0 mg/kg, 6.0 mg/kg, 9.0 or 10.0 mg/kg bwt and placebo of each 16 patients. The findings are summarized in Tables 1 and 2. Sixteen cases with an average EPG of 481 (127~1,969) were treated with amidantel in a single dose of 3.0 mg/kg bwt. 12 cases became negative for *A. duodenale* eggs by the Stoll's egg counts and concentration method during the first follow-up period of 14th to 16th day after treatment, but 10 of these had negative fecal egg counts again and absence of eggs in feces examined by the concentration method during the second follow-up period of 28th to 30th day after treatment. Therefore the cure rate was shown as 62.5 per cent, but 6 cases in whom eggs were found had counts of less than 100 eggs per gram of feces. The average egg reduction rate was 99.5 per cent. In the coproculture of these 6 cases, all the larvae recovered were identified as the larvae of *A. duodenale*. A total number of 195 adult worms of *A. duodenale* were recovered from 14 out of 16 treated patients. In the assessment of the efficacy in

Table 1. Anthelmintic effect of a single dose of amidantel (Bay d 8815) against *Ancylostoma duodenale* infection

Dosages (mg/kg)	No. of patient	Pre-Tx mean E.P.G.* (range)	No. of patient cured	Egg reduction rate(%)	Cure rate (%)	No. of worms collected
3.0	16	481(127~1,969)	10	99.5	62.5	195
6.0	16	631(257~4,343)	15	99.9	93.8	351
9.0 or 10.0	16	675 (86~5,037)	14	99.9	87.5	333
Placebo	16	437(213~1,489)	0	10.5	0.0	0

* Geometrical mean value of EPG.

Table 2. Evaluation of efficacy of amidantel (Bay d 8815) against *Ancylostoma duodenale* infection

Dosages(mg/kg)	No. of patient	Evaluation of efficacy					Egg reduction rate(%)
		Excellent	Good	Fair	Poor	Failure	
3.0	16	10	2	4	0	0	99.5
6.0	16	15	0	1*	0	0	99.9
9.0 or 10.0	16	14	0	2*	0	0	99.9
Placebo	16					16	10.5

* Each one case was mixed infection of *A. duodenale* and *N. americanus*, but only *N. americanus* was remained after treatment.

this dosage group, 10 cases were cured completely with the evaluation of *excellent* therapeutic efficacy, and 2 cases were evaluated as *good* and 4 cases were evaluated as *fair* therapeutic efficacy on the follow-up study on the days of 28th to 30th day after treatment.

Each 16 patients receiving a single dose of 6.0 mg/kg and 9.0 or 10.0 mg/kg bwt of amidantel have shown 631 (257~4,343) and 675 (86~5,037) of mean pretreatment EPG of *A. duodenale* respectively. In the second group of 16 patients, receiving a single dose of 6.0 mg/kg bwt, all cases except one were negative eggs in the stools collected on the 14th to 16th and 28th to 30th day after treatment by the examinations of Stoll's egg counts and concentration method. Only one case had shown a small number of eggs by the concentration method in both follow-up examinations. In this case coproculture was made, and only the larvae of *Necator americanus* were found. The overall egg reduction rate was shown as 99.9 per cent. A total number of 351 adult hookworms were collected from 15 of 16 treated patients. Therefore 15 out of 16 cases (93.8% cure rate) were assessed as *excellent* therapeutic efficacy, and only one case was evaluated as *fair* therapeutic efficacy.

14 out of 16 patients received 9.0 or 10.0 mg/kg bwt were negative eggs in the stools examined on the 1st and 2nd follow-up study, but only 2 cases were detected eggs in their stools by concentration method. The stools of these 2 cases were made for coproculture, and only one case had shown the larvae of *A. duodenale* and the other case had shown the larvae of *N. americanus*. The overall egg reduction rate was shown as 99.9 per cent. A total number of 333 adult hookworms were collected from the stools of 16 treated cases. Therefore 14 out of 16 cases (87.5% cure rate) were assessed as *excellent* and 2 cases were evaluated as *fair* therapeutic efficacy.

On the other hand, 16 cases with an average EPG of 437 (213~1,489) were given placebo with the dosis as the same as corresponding body weight of receiving dosis of 10.0 mg/kg bwt of amidantel. After the medication with placebo, all cases were still shown the eggs in their stools examined on the 1st and 2nd follow-up study. Only 10.5 per cent of the egg reduction rate was shown on the 2nd follow-up study. There was not any cured case. All the stools were made for coproculture, and the larvae recovered were identified as the larvae of *A. duodenale*.

The patients were observed to determine and record the incidence, type and severity of side effects. Clinical hematology, biochemical tests of liver and renal functions, urinalysis, ECG and cranial nerve functions in 64 patients were performed before and after treatment. No changes were observed in these tests after treatment suggesting any influence due to amidantel. In

Table 3. Incidence of side effects of amidantel (Bay d 8815)

Symptoms	Dosages (a single dose) (mg/kg)			
	3.0	6.0	9.0 & 10.0	Placebo
No. of patients examined	16	16	16	16
No. of patients without symptoms	8	6	2	10
No. of patients with symptoms (%)	8(50.0%)	10(62.5%)	14(87.5%)	6(37.5%)
Headache	7	6	10	1
Nausea	2	2	5	3
Dizziness	1	4	8	1
Abdominal discomfort	3	5	4	1
Fatigue	2	6	4	2
Fever	1	1	1	0

a few patients showed abnormalities in these tests prior to treatment because of co-existing disease, none of patients were made worse by the drug. The kinds and numbers of side effects including slight complaints, which were observed immediately after treatment with any of these 4 dosages are summarized in Table 3.

Adverse reactions consisted mainly of headache, nausea, dizziness, abdominal discomfort and fatigue *etc*. But none of these symptoms was so severe to require bed-rest or withdrawal of the drug. Among 16 patients treated with 3.0 mg/kg bwt with amidantel, 8 (50.0%) cases complained side effects. 10 (62.5%) of 16 patients received 6.0 mg/kg bwt of the drug complained side effects. In the higher dose of 9.0 or 10.0 mg/kg bwt of amidantel, 14 (87.5%) out of 16 patients complained side effects. However, even placebo groups complained side effects in 6 (37.5%) out of 16 cases. In the above findings, the higher incidence of side effects were observed in the higher doses group.

Therefore the final assessment of tolerance of amidantel in the groups of 4 different dosages was shown in Table 4.

In the groups receiving placebo and 3.0 mg/kg bwt of amidantel, all cases were assessed as excellent tolerance of amidantel. But the groups consisting each 16 patients receiving 6.0 mg/kg bwt and 9.0 or 10.0 mg/kg bwt of amidantel were assessed as excellent tolerance in 12 and 9 cases, and as good tolerance in 4 and 7 cases respectively. There was no case assessed as fair or poor tolerance of amidantel in any groups.

2. The second trial (Dose confirming)

The second trial was carried out as open controlled study and was designed to confirm the findings of the toleration and efficacy of

Table 4. Final assessment of tolerance of amidantel (Bay d 8815) against *Ancylostoma duodenale* infected patients

Dosages(mg/kg)	No. of patient	Assessment				Not assessible
		Excellent	Good	Fair	Poor	
3.0	16	16	0	0	0	0
6.0	16	12	4	0	0	0
9.0 or 10.0	16	9	7	0	0	0
Placebo	16	16	0	0	0	0

Table 5. Anthelmintic effect of a single dose of amidantel (Bay d 8815) against hookworm infections

Dosages (mg/kg)	Species	No. of patient treated	Pre-Tx mean* EPG(range)	No. of patient cured	Mean egg reduction rate(%)	Cure rate(%)	No. of worms collected
8.0	A.d.**	23	436(262~709)	22	99.8	95.7	322
	A.d. & N.a.	3	469(251~1,051)	1	98.9	33.3	33(A.d.) 28(N.a.)
	N.a.***	6	499(277~1,688)	0	98.1	0	174
		32	450(251~1,688)	23	99.6	71.9	557
6.0	A.d.	29	206(19~1,228)	28	99.4	96.6	199
	A.d. & N.a.	1	304	0	88.2	0	4(A.d.) 1(N.a.)
	N.a.	1	348	0	64.7	0	4
		31	212(19~1,228)	28	99.3	90.3	208
5.0	A.d.	11	130(46~593)	10	99.1	90.9	30
	A.d. & N.a.	2	335(322~348)	1	97.7	50.0	7(A.d.) 4(N.a.)
		13	151(46~593)	11	99.0	84.6	41

* Geometrical mean value of EPG ** *Ancylostoma duodenale* *** *Necator americanus*

amidantel using the dosis which proved most effective in the first trial. Using the dosis of 6.0 mg/kg amidantel which proved most effctive in the first trial, another 31 patients infected by one or both hookworm species were treated. In addition to this dosis, a single dose of 8.0 mg and 5.0 mg per kg of body weight of amidantel were also given to the other 32 and 13 patients respectively in order to confirm the most effective dosis.

In the second trial total of 76 patients infected with one or both hookworm species were treated with amidantel in a single dose of 8.0 mg/kg, 6.0 mg/kg, and 5.0 mg/kg bwt. The detailed data concerning the egg counts and coproculture before and after (14th and 30th day) treatment together with the number and species of expelled adult worms during 3 consecutive days after medication are shown in Table 5.

Thirty-two cases of hookworm infections with an average EPG of 450 (251~1,688) were treated at a dosis of 8.0 mg/kg bwt of amidantel. 23/32 (71.9%) patients were negative in egg counts, concentration technique and coproculture at day 30 post-treatment examination. Of the 9 failures 3 were positive in egg counts, 6 by concentration technique and all by coproculture. The larvae recovered in the 9 failures by coproculture, were identified as the larvae of *Necator americanus* in 8 and those of *Ancylostoma duodenale* in one case. Thus among 32 cases, there were 23 cases of a pure *A. duodenale* infection, 6 cases of a pure *N. americanus* infection and 3 cases of a mixed infection of *A. duodenale* and *N. americanus*. 22/23 (95.7%) cases with a pure infection of *A. duodenale* were negative in egg counts, concentration technique and coproculture at post-treatment day 30 examination. The one failure was positive in concentration technique and coproculture. Therefore the mean egg reduction rate was shown 99.8%, and a total number of 322 (male worms, 120; female worms, 202) adult worms were recovered from 19 out of 23 patients. However 6 cases with a pure infection of *N. americanus* were not cured completely and in 3 cases of mixed infection of *A. duodenale* and *N. americanus*, only one case was cured. But the mean egg

reduction rates were shown as 98.1% and 98.9% respectively. A total number of 174 (male worms, 71; female worms, 103) adult worms of *N. americanus* were recovered from all 6 cases and 33 adult worms of *A. duodenale* and 28 adult worms of *N. americanus* were recovered from the 3 treated cases who were infected with the both species of hookworms.

Of the 31 cases who were treated with a single dose of 6.0 mg/kg bwt amidantel, 28 (90.3%) were negative in egg counts, concentration technique and coproculture at day 30 post-treatment examinations. 29/31 cases were infected with a pure infection of *A. duodenale* and each one case was infected by pure *N. americanus* and mixed infection of both species. Only one case out of 29 cases with a pure infection of *A. duodenale* was positive in egg counts at the follow-up examination. Therefore the mean egg reduction rate was shown 99.4% and the cure rate was 96.6%. The total number of recovered adult worms were counted 199 (male worms, 70; female worms, 129) from 25 cases out of 29 cases treated with amidantel. In each one case of pure infection of *N. americanus* and mixed infection of both species, all cases were not cured completely, but the mean egg reduction rates were 88.2% and 64.7% respectively. 4 adult worms were recovered from a case infected by pure *N. americanus* and 4 adult worms of *A. duodenale* and 1 worm of *N. americanus* were recovered from a case infected by both species.

In the dosis of 5.0 mg/kg bwt of amidantel, 11 out of 13 hookworm cases were infected by a pure *A. duodenale* and the other 2 cases were infected with a mixed infection of both species. 10 (90.9%) out of 11 cases with a pure infection of *A. duodenale* and one out of 2 cases with a mixed infection of both species were negative in the follow-up period. The mean egg reduction rates were 99.1% and 97.7% respectively. A total number of recovered adult worms were 30 (male worms, 12; female worms, 18) from 9 out of 11 cases, and 7 adult worms of *A. duodenale* and 4 *N. americanus* were found from 2 cases of mixed infection of both species.

Side effects have occurred in frequencies as 23.1 per cent at the dose rate of 5.0 mg/kg, 54.8 per cent at 6.0 mg/kg, and 43.8 per cent at 8.0 mg/kg bwt of amidantel in this trial.

Table 6. Incidence of side effects of amidantel (Bay d 8815)

Symptoms	Dosages (a single dose) (mg/kg)		
	5.0	6.0	8.0
No. of patients examined:	13	31	32
No. of patients without symptoms:	10	14	18
No. of patients with symptoms (%):	3 (23.1%)	17 (54.8%)	14 (43.8%)
Headache	1	10	6
Nausea	0	0	7
Dizziness	1	13	10
Abdominal discomfort	1	9	2
Fatigue	0	2	3
Fever	1	0	2
Vomiting	0	2	0
Urticaria	0	0	2

Table 7. Evaluation of efficacy of amidantel (Bay d 8815) against other intestinal parasites

	Dosages (mg/kg)	No. of patient treated	Pre-Tx mean* E.P.G. (range)	No. of patient cured	Mean egg reduction rate (%) (range)	Cure rate (%)	Total No. of worms collected
Ascaris lumbricoides	3.0	11	2,138(283~8,454)	7	90.0 (0~100)	63.6	22
	5.0	7	952(200~8,516)	6	99.9(98.2~100)	85.7	10
	6.0(Ⅰ)**	11	1,120 (13~4,641)	10	95.9(54.4~100)	90.9	36
	6.0(Ⅱ)***	29	2,141(55~38,573)	27	99.9(95.1~100)	93.1	129
	8.0	21	2,495(126~9,683)	18	99.9(99.2~100)	85.7	135
	9.0 or 10.0	8	932 (21~6,840)	7	99.5(95.9~100)	87.5	31
Trichuris trichiura	3.0	12	223 (31~1,270)	0	64.1 (0~88.1)	0	0
	5.0	11	290 (5~2,882)	1	64.4 (0~100)	9.1	0
	6.0(Ⅰ)**	11	168 (8~1,036)	1	69.0 (0~100)	9.1	9
	6.0(Ⅱ)***	22	102 (5~416)	2	76.3 (0~100)	9.1	15
	8.0	20	210 (5~1,132)	1	53.1 (0~100)	5.0	1
	9.0 or 10.0	10	246 (100~358)	0	74.2 (0~96.9)	0	19
Metagonimus yokogawai	6.0(Ⅱ)	2	783 (654~832)	2	100.0	100.0	—

* Geometrical mean value of EPG; ** 1st trial; *** 2nd trial

However their severity has usually been assessed as mild or moderate. Headache, nausea, dizziness and abdominal discomfort were frequently reported (Table 6). Clinical hematology, biochemical tests, urinalysis and ECG were performed before and after treatment in all treated cases except 13 patients who were given a single dose of 5.0 mg/kg of amidantel. In the result no abnormalities were revealed.

The therapeutic effects with a single dose of amidantel with the various doses to the other intestinal helminths frequent in the trial areas such as *Ascaris lumbricoides*, *Trichuris trichiura* and *Metagonimus yokogawai* are shown in Table 7. A total number of 87 patients with *A. lumbricoides* were treated with either 3.0, 5.0, 6.0, 8.0 and 9.0 or 10.0 mg/kg bwt of amidantel. The high anthelmintic effects were observed in each dosis of amidantel. In all doses groups except 3.0 mg/kg dose group, the mean egg reduction rates and cure rates were shown over 95 and 85 per cent respectively. A single dose of 3.0, 6.0 and 9.0 or 10.0 mg/kg bwt of amidantel in the first trial cured 7/11 (63.6%), 10/11 (90.9%) and 7/8(87.5%) respectively. In the second trial, 6/7 (85.7%) cured by a single dose of 5.0 mg/kg, 27/29 (93.1%) by 6.0 mg/kg and 18/21 (85.7%) by 8.0 mg/kg bwt of amidantel. However 99.9 per cent of mean egg reduction rate was revealed in all treated groups. On the other hand, 86 patients with *T. trichiura* were also observed the efficacy at the same doses of amidantel, but no significant activity was noted against *T. trichiura*. Though the mean egg reduction rates were shown ranging from 53.1 to 76.3 per cent, only 0 to 9.1 per cent of cure rates were observed. However several adult worms were recovered from the stools of treated patients after medication. In two cases with *Metagonimus yokogawai* infection, all were cured completely by a single dose of 6.0 mg/kg bwt of amidantel.

DISCUSSSION

This study is the first application for the clinical investigation of hookworm infection with amidantel (Bay d 8815). Amidantel is a new

anthelmintics. In animal experiments it has been proved to be effective against hookworms, *Toxocara canis* and *T. cati* with a single oral dose of 25 mg/kg resulting in a 97 to 100 per cent parasite reduction (Wollweber *et al.*, 1979).

The assessment of the new substance should take into account its safety, absolute cure rate, effect on worm burden, and patient acceptability. According to Davis (1972), the evaluation of anthelmintic efficacy requires detailed correctly designed trials. Estimates of drug efficacy against *A. duodenale* and *N. americanus* should be based on worm counts and identification after anthelmintics. It is necessary to undertake pretreatment egg counts and fecal culture in order to identify pure *A. duodenale* infection, pure *N. americanus* infection or mixed infections.

In this study, three separate pretreatment stool samples were examined by Stoll's egg counting method. Of each stool 4 replicates of the same weight were examined. The purpose of these replications is to reduce measurment errors to an acceptable minimum and achieve a precision lacking in a single measurement. Prior to treatment, identification of hookworm species by fecal culture was made twice. Immediately after treatment, worm count was carried out with 3 consecutive stools. The follow-up examinations carried out by repeated and replicated examinations over three consecutive days performed at either 14 to 16 days, or 28 to 30 days or both. The assessment of efficacy was carried out by two steps in the follow-up studies. If eggs were not found in all aliquots, in either egg counts or concentration method during the 3 consecutive days from 14th to 16th day after treatment, further follow-up examination was proceeded to the second step, in which the same procedure as the first step was performed during the days from 28th to 30th day after treatment.

In the results of the first trial in the present study, a single dose of 3.0 mg/kg bwt of amidantel cured only 63.0 per cent of 16 cases with *A. duodenale*, but the mean egg reduction rate was shown as 99.5 per cent. However, 93.8 and 87.5 per cent cure rates were obtained respectively when each 16 patients received 6.0 mg/kg and 9.0 or 10.0 mg/kg bwt of amidantel, but in both dosage groups the mean egg reduction rate was shown 99.9 per cent. In the second trial a total of 76 patients infected with one or both hookworm species were treated with amidantel in a single dose of 8.0, 6.0 and 5.0 mg/kg bwt.

Using these only one case in each group was failed in complete cure. Therefore, 90.9 to 96.6 per cent of *A. duodenale* infected patients were cured and their mean egg counts were reduced 99.1 to 99.8 per cent. In *Necator* infection, however, no one case was cured completely in 6 patients in the dose of 8.0 mg/kg bwt and one patient in the dose of 6.0 mg/kg bwt of amidantel. But the mean egg reduction rates were 98.1 and 64.7 per cent respectively. On the other hand, in the mixed infections with *Ancylostoma* and *Necator*, only two cases out of 6 patients received 5.0, 6.0 or 8.0 mg/kg were cured. But the mean egg reduction rates were 88.2 to 98.9 per cent and a considerable numbers of adult worms of *A. duodenale* and *N. americanus* were recovered from all treated cases. In the follow-up studies, all of the *Ancylostoma* were removed, but the four of the patients still harbored *Necator* after therapy. According to Botero (personal communication), 3 out of 5 patients infected with pure *Necator* were cured by 3 doses of 3.0 mg/kg bwt of amidantel in a single day and their mean egg counts was reduced 99.8 per cent. It is evident that amidantel is more active against *Ancylostoma* than *Necator*. Although cure rates in *Necator* infection are lower than in *Ancylostoma* infection, the egg reduction rates were shown high.

Therefore amidantel shows substantial activity

against *Necator americanus*.

The results in this study were similar or somewhat superior to those obtained in previous clinical trials with other drugs for treatment of hookworm infection. Bell (1970) noted that 98 per cent cure rate was obtained in 53 *A. duodenale* infected patients treated with a single dose of 17.6 mg/kg bwt of pyrantel pamoate. However, Cervoni (1970) showed 30 to 75 per cent cure rate in *N. americanus* patients who were treated with pyrantel pamoate in a single dose of 10 mg/kg bwt. The relative efficacy against *A. duodenale* and *N. americanus* has been reported by Yokogawa *et al.* (1970), who obtained a cure rate of 90 per cent for *A. duodenale* and 78.5 per cent for *N. americanus* with a single dose of 20 mg/kg bwt of pyrantel pamoate. Hsieh and Chen (1970) cured also 91 per cent of 35 patients with *A. duodenale* and 71 per cent of 21 patients with *N. americanus* with a single dose of 10 mg/kg bwt of pyrantel pamoate. A single dose of 10 mg/kg bwt of pyrantel pamoate cured 93.8 per cent of 43 patients infected with *A. duodenale* and 64.0 per cent of 25 infected with *N. americanus* (Rim *et al.*, 1973). Lim *et al.* (1975) obtained similar result, *i.e.* 90 per cent cure rate obtained in 20 patients infected with *A. duodenale*, whereas 1 out of 2 *N. americanus* infected cases and 8 out of 13 (61.5%) patients with mixed infections of *A. duodenale* and *N. americanus* was cured. However 2 or 3 successive daily doses of pyrantel pamoate (10 or 20 mg/kg) were appreciably more effective in the cure of infections with *N. americanus* (Rim *et al.*, 1973).

On the other hand, Hahn *et al.* (1960) cured 98 per cent of 153 patients with *A. duodenale* with a single dose of 2.5g of bephenium hydroxynaphthoate. Young *et al.* (1960), however, produced no cures and only a 67 per cent of egg reduction rate in 12 infections with *N. americanus* using same dosage of bephenium base. Ahmad and Ghulam (1959) achieved also a cure rate of 83 per cent in 74 patients who harbored both *A. duodenale* and *N. americanus*. Lim *et al.* (1975) obtained 88.2 per cent of cure rate in 17 *A. duodenale* infections with a single dose of 2.5 g of bephenium hydroxynaphthoate, but 62.5 per cent cure rate was obtained in 8 *N. americanus* infections, 66.7 per cent in 9 mixed infection cases and 13 out of 17 (76.5%) in unspecified infestations.

Therefore, amidantel is at least as effective as pyrantel pamoate and probably more effective than bephenium hydroxynaphthoate. Likewise it is also very effective for the treatment of *Ascaris* infection. A single dose of 6.0 mg/kg bwt of amidantel cured 10 (90.9%) out of 11 cases and 27 (93.1%) out of 29 cases with *A. lumbricoides* with 95.9 and 99.9 per cent of mean egg reduction. The doses of 8.0 and 9.0 or 10.0 mg/kg of amidantel cured also 85.7 and 87.5 per cent out of 21 and 8 cases infected with *A. lumbricoides*, but the mean egg reduction rates were 99.9 and 99.5 per cent respectively. No significant activity was noted against *Trichuris trichiura*. However amidantel, given in a single dose of 6.0 mg/kg, shows complete cure against *Metagonimus yokogawai* infection.

Side effects include headache, nausea, dizziness, abdominal discomfort, fatigue and vomiting. They were usually mild and transient, and appeared to be dose dependent, occurring largely in patients receiving more than 6.0 mg/kg bwt.

With regard to dosage, however, in the present study 6.0 mg/kg of amidantel was found to be more effective than the doses of 8.0 to 10.0 mg/kg and also more well tolerated at the dose level of 6.0 mg/kg bwt.

In the pharmacokinetics and toxicological studies (personal communication; Bayer AG. Wuppertal. West Germany), following oral application of amidantel to two dogs and two sheep, 17 and 24 per cent of the dose were excreted in the

urine as the deacetylated *p*-amino-phenyl-acetamidine product, within 24 and 48 hours respectively. After oral application of amidantel maximum blood levels of the metabolite were reached within 2 to 6 hours in dogs and 5 to 6 hours in sheep. Acute toxicity was tested in mouse, rat, rabbit, cat and dog. While the LD_{50} in mice, rabbits, cats and dogs is about in the same range (*ca.* 500 to 1,000 mg/kg) after oral administration, rats were found to tolerate noticeably higher doses (4,693～5,698 mg/kg). The subacute toxicity test with amidantel in dogs has shown that daily doses of 30 mg/kg bwt, given orally for 4 weeks, are as well tolerated without any adverse reactions. Even after 100 mg/kg bwt only slight symptoms in the form of salivation were observed after treatment in one of the 4 dogs. Neither laboratory tests nor autopsies and histopathological examinations revealed any evidence of specific toxic damages (Wollweber *et al.*, 1979).

The clinical examinations for hematology, blood biochemistry and urinalysis as well as ECG in the present study did not show any evidence of damages to the patient by amidantel in all dosage groups.

The good effectiveness of amidantel in the treatment against *A. duodenale* and *A. lumbricoides* infections in this study together with its excellent toleration suggest amidantel may become the drug of choice for these infections.

SUMMARY

A new anthelmintic, amidantel (Bay d 8815), an acetylated *p*-amino-phenyl-acetamidine was tried in 140 patients with *Ancylostoma duodenale* and other helminth infections. In the first trial, each 16 cases in 64 patients with *A. duodenale* were treated with 3.0, 6.0 and 9.0 or 10.0 mg /kg body weight of amidantel including placebo control. Another 76 patients infected with hookworms and other helminths were treated with 5.0, 6.0 and 8.0 mg/kg body weight of amidantel in the second trial.

In order to assess the efficacy and safety of the drug, follow-up examinations by repeated and replicated examinations over three consecutive days were performed at 14 to 16 days and 28 to 30 days after treatment. And complete laboratory studies including ECG were carried out before and one day after the medication.

In the results, it was confirmed that amidantel is very effective against *A. duodenale* as well as *Ascaris lumbricoides*. With regard to dosage, a single dose of 6.0 mg/kg body weight of amidantel was found to be the most effective and well tolerated than the other dosages employed. In a single dose of 6.0 mg/kg body weight the cure rates were 93.8 and 96.6 per cent for *A. duodenale* infection and 90.9 and 93.1 per cent for ascariasis in the first and second trials respectively. Relatively significant activity was also observed against *Necator americanus* at the dosages employed, however it was not superior to other drugs currently use. No significant activity was noted against *Trichuris trichiura*.

Side effects including headache, nausea, dizziness and abdominal discomfort were usually mild and transient. No significant changes attributable to therapy were observed in hematology, blood biochemistry and urinalysis as well as ECG.

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＝國文抄錄＝

十二指腸蟲에 대한 Amidantel (Bay d 8815)의 驅蟲效果

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最近 새로이 開發된 驅蟲劑 Amidantel(Bay d 8815)을 140例의 十二指腸蟲 및 他蠕蟲類 感染者에 投藥하여 그 驅蟲效果를 檢討하였다.

第1次 投藥試驗에 있어서 61例의 十二指腸蟲感染者中 各各 16例씩에 Amidantel을 3.0, 6.0 및 9.0 혹은 10.0 mg/kg을 單回 投藥하였고 對照群은 僞藥(placebo)을 投藥하였다. 그리고 第2次 投藥試驗에 있어서는 76例의 鉤蟲 및 他蠕蟲의 同時感染者에 대하여 Amidantel을 5.0, 6.0 및 8.0 mg/kg를 單回 投藥하여 各各 驅蟲效果를 比較檢討하였다.

驅蟲效果는 投藥前 3回 糞便檢査에서 얻은 EPG와 投藥後 14～16日과 28～30日에 各各 3日間 反復糞便檢査를 실시하여 얻은 成績을 比較하여 判定하였다.

本劑의 副作用을 投藥後 3日間 觀察하였고 血液像, 血液生化學的 檢査와 尿檢査를 投藥前과 投藥 24時間後에 실시하여 比較하였고 心電圖도 投藥前後에 실시하여 比較하였다.

그 結果 Amidantel은 十二指腸蟲과 蛔蟲에 대하여 특히 그 驅蟲效果가 좋다는 것이 證明되었고 6.0 mg/kg의 單回投藥群이 他投藥群에 比하여 더 좋은 驅蟲效果를 보였다. 即 十二指腸蟲에 대하여 93.8% 및 96.6%의 治療率을 第1次 및 第2次 投藥試驗에서 各各 얻었고 蛔蟲에 대하여는 90.9% 및 93.1%의 治療率을 各各 第1次 및 第2次 投藥試驗에서 얻었다. Amidantel은 아메리카鉤蟲에 대하여 比較的 좋은 驅蟲效果를 나타내었으나 他藥劑에 比하여 더 우수하지 않았고 鞭蟲에 대하여는 거의 驅蟲效果가 없었다.

副作用으로서 Amidantel 6.0mg/kg 單回投藥 하였을 때 輕微한 頭痛, 惡心, 眩氣症 및 腹痛등이 一時的으로 있었으나 投藥前後에 있어서 血液像, 血液生化學的와 尿檢査 및 心電圖의 變化는 볼 수 없었다.