BEPHENIUM HYDROXYNAPHTHOATE IN TREATMENT OF ASCARIASIS

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In the course of the clinical trials with bephenium compounds against hookworm in Ceylon (Goodwin, Jayewardene, and Standen, 1958) it was found that concurrent infections with roundworm were also cleared in the majority of cases treated. Early in 1959 bephenium hydroxynaphthoate was used, in divided doses, over a period of days, to test its efficacy against whipworm infections. The action of the drug against roundworm was again observed; a large number of children passed roundworms on the first day of treatment, some within half an hour of taking the drug. As the drug was employed in a much smaller dosage than for hookworm infections its action against roundworm appeared to be considerable.

In view of this it was decided to determine the minimum effective single dose for mass anti-ascariasis treatment, and the minimum dose required for total clearance of infection.

Material and Methods

In the hookworm trials it was established that the effective dose of the bephenium compounds was the same for adults and children. Children were therefore selected for this trial as they were more likely to have infections with roundworm. At the start children residing in state homes and orphanages were selected as they were in organized groups that could be supervised. Later, children from homes in poor sanitary conditions were treated. These homes, however, were in groups which were conveniently placed for mass treatment. Subsequently a few adults, mainly patients from the General Hospital, Colombo, were included in the series.

All subjects were taken at random and divided into groups. The only precaution taken was to see that each group had roughly the same age distribution.

Faecal samples were collected in small cartons. These were first examined by the direct saline smear method. Those found positive had an ova count by a modified Stoll method (Stoll and Hausheer, 1926). Follow-up examinations were made on the fourth day after treatment. In a few instances the follow-up was delayed, but in none did the delay exceed two weeks. The follow-up samples were examined by the direct saline smear method. If found negative they were then examined after concentration, using the M.I.F. technique (Blagg, Schlegel, Mansour, and Khalaf, 1955). The positive samples had an ova count done in duplicate.

In assessing the results of treatment, all follow-up specimens which were negative even after concentration were regarded as being 100% cleared of infection. Those negative on direct smear but positive on concentration were estimated to have fewer than 200 eggs per ml. of faeces, and were also grouped as being 100% cleared.

In those positive on direct smear the percentage reduction on the original egg count was determined, and is referred to as "percentage clearance."

Bephenium hydroxynaphthoate ("alcopar") was kindly supplied by Messrs. Burroughs Wellcome Ltd. Different preparations were tried on various groups to determine the best method of masking the bitter taste of the drug. Some groups had plain granules suspended in water, while others had the drug in a 3.5% sugar solution flavoured with essence of lemon. A peppermint-flavoured suspension and chocolate-coated granules were used on other groups. These two preparations were supplied as such by the firm. (In practice, we found a sweet, such as a fruit-drop, very useful for tempting small children to take the drug.)

The drug was given at different times of the day. Some had it first thing in the morning on an empty stomach, the morning meal being taken about one to one and a half hours later. Others had the drug last thing at night, about three hours after their last meal. When two doses of the drug were given on the same day, the second dose was given at about 3 p.m., three to four hours after the midday meal. In no case was a purge employed.

Results

In all, 396 subjects were treated. The dose employed varied from group to group. Infection in the children varied from light to very heavy, the highest count being 265,000 eggs per ml. of faeces. The Chart shows the distribution of infection. Table I shows the percentage clearance of eggs in relation to the dose employed.

When a dose of 0.625 g. was used, only 35.7% of cases (28 treated) showed over 80% clearance. More

TABLE I.—Dose and Percentage Clearance in Egg Count

Dose (g. of Bephenium Base)*	No. Treated	[Clearance 80% and Over	
		No.	%
0.625	28	10	35.7
1.0	48	27	56.2
1.25	55	39	70.9
1.66	59	38	64.4
2.0	47	36	76.6
2.5 { with syrup, etc.	37	31	83.8
2.5 { chocolate-coated	19	14	73.7
2 x 1.25	54	48	88.9
2 x 1.66	49	46	94.0

* Dose throughout is in terms of bephenium base. Corresponding dose in terms of bephenium hydroxynaphthoate granules is double this figure.

TABLE II.—*Distribution of Cases with More than 80% Clearance in Relation to Initial Egg Count and Dose*

Initial Egg Count in 1,000's	Dose (g.)																	
	0.625		1.0		1.25		1.66		2.0		2.5*		2.5†		2 × 1.25		2 × 1.66	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 5	6	50	13	54	11	46	13	69	20	67	11	91	7	43	7	71	10	90
5 < 10	4	50	9	67	9	78	12	42	10	70	7	57	2	50	11	82	10	90
10 < 20	10	40	6	50	14	71	16	69	8	100	9	90	7	100	13	92	11	91
20 < 30	3	0	3	0	5	80	5	60	4	100	4	100	3	100	8	100	3	100
30 < 40	—	—	7	71	7	71	5	60	2	100	3	100	—	—	5	80	9	100
40 and over	5	20	10	50	9	89	8	87	3	100	3	66	—	—	10	100	6	100
Total	28	36	48	56	55	71	59	64	47	77	37	84	19	74	54	89	49	94

* Granules given with syrup or water. † Chocolate-coated granules given with water.

children were not treated with this dose as it appeared inadequate.

With a dose of 1 g. a larger number of cases had 80% clearance, but there were many failures in persons with initial counts of 20,000 or more eggs per ml. of faeces. When a dose of 1.25 g. was employed, the clearance obtained in cases with initial counts of 20,000 or more eggs per ml., was dramatic. The higher the count the more effective was the clearance. 71% of cases treated had more than 80% clearance. The majority of failures in this group were among those with counts of fewer than 20,000 eggs per ml. of faeces.

The results obtained with 1.66 g. appeared to be less satisfactory than those obtained with 1.25 g., but the difference was not statistically significant. Generally, however, Table I shows that with increasing dosage an increase in the number with 80% clearance of infection is to be expected. When two doses of 1.25 g. or two doses of 1.66 g. were given on the same day, 80% of clearance was obtained in 90% and 94% of subjects respectively.

Table II shows the percentage clearance obtained with different doses in relation to the initial egg count. It was mentioned earlier that with doses of 1.25 g. or more the majority of cases with counts of 20,000 or more eggs per ml. had over 80% clearance of their infection. This is clearly seen in Table II. This group, however, had two cases with egg counts between 40,000 and 50,000. One had over 80% clearance, the other had 68.5% clearance. In the same group, of those with low counts of fewer than 5,000 eggs (11 cases), only 46% had 80% clearance. But at all higher infection levels, 70% or more had over 80% clearance of infection. With lower doses less than half the subjects had 80% clearance of infection, whatever the original level of infection.

Table III shows the incidence of vomiting in relation to the dose. It will be seen that the incidence of vomiting increased with the rise in the dose from

0.625 g. to 1.25 g. However, the two smallest doses were ineffective for roundworm, and therefore the lower incidence of vomiting with these can be disregarded for practical purposes. With doses above 1.25 g. the incidence of vomiting was not significantly different except for the dose of 2.5 g. of chocolate-coated granules and that of 2 × 1.66 g., where the vomiting was significantly less. The former result is probably due to the chocolate being an effective mask for bitterness. The latter result cannot be accounted for so easily. It may be due to several other factors (see below).

In relation to age, the incidence of vomiting was significantly greater in children under 4 years old in all groups except those receiving the ineffective doses of 0.625 g. and 1 g. Of 325 children over 4 years, 70 vomited and of 71 children under 4 years 29 vomited. (The chocolate-coated granules were bulky and were not given to children under 4 years of age.)

The time of administration did not have an observable effect on the results obtained, except that vomiting was more likely to occur if a meal was taken immediately after or before the drug. When two doses of the drug were given on the same day the incidence of vomiting was not significantly different between those having the midday meal three hours before the second dose and those having it four hours before.

The results show that 1.25 g. can be regarded as the minimum effective dose, because with this dose 86% of the children passed worms, 71% had over 80% clearance, and practically all those with initial counts of more than 20,000 eggs had also over 80% clearance.

Discussion

In countries like Ceylon, where there is no immediate prospect of improving prevailing insanitary conditions or cleaning up seeded soils, the only means of preventing children from being overburdened with ascarides is by regular treatment. For example, in our previous hookworm and whipworm series, almost all patients who had incidentally been cleared of roundworm infection were subsequently found to have unfertilized roundworm ova in their stools at the end of four weeks. We also had the opportunity of examining over 100 children six months to one year after they had been treated with full doses of piperazine citrate ("antepar"). (Most of them had had buphenium compounds as well.) Practically all the children were found to be infected again to about their original level. This could only mean that reinfection is continually occurring, as judged by the known resistance and longevity of the roundworm egg. In these circumstances the value of administering massive doses of anthelmintics for complete clearance of infection is of questionable value. This is particularly so with regard to mild infections.

TABLE III.—*Vomiting in Relation to Dose*

Dose (g.)	No. Treated	Vomiting	
		No.	%
0.625	28	3	10.7
1.0	48	8	16.7
1.25	55	13	23.6
1.66	59	17	28.8
2.0	47	12	36.2
2.5 with syrup, etc.	37	12	32.4
2.5 chocolate coated	19	1	5.3
2 × 1.25 { peppermint flavoured	28	16	57.1
2 × 1.25 { lemon flavoured	26	5	19.2
2 × 1.66	49	8	16.3
Total	396	100	25.0

The dose of bephenium hydroxynaphthoate recommended by us is small, is acceptable to all ages, causes very little vomiting, and is effective. If a more thorough clearance is sought, two such doses should more than suffice, given either on the same day or on two successive days.

In the treatment of hookworm infection, where the worms are closely attached to the bowel wall and where there must be an empty bowel to ensure close contact between worm and drug, it is essential that the drug be given first thing in the morning. In roundworm infection also, the best time for administering the drug is in the morning, but it may also be given last thing at night after an early dinner. Where two doses are given on the same day, it is best to give the midday meal early, at about 11 a.m., and the second dose about four hours later. Here it must be noted that when a meal is taken shortly before or soon after the drug there is a greater tendency to vomit.

In our experience the best preparation was the freshly prepared suspension in lemon-flavoured syrup. Most children accepted this, and some of the 2-year-olds even sipped it at leisure. (The other preparations are discussed in relation to the incidence of vomiting.)

In treatment of ascariasis with bephenium hydroxynaphthoate the daily programme of the school child is upset only by the passage of worms. Worms are passed from within half an hour of taking the drug to three days later. They are generally alive when passed, but by about 24 hours the majority are dead and the rest only feebly active. A few children stated that they vomited coils of small worms. We did not have an opportunity of examining these, but they were presumably developing roundworms en route in the stomach or the upper reaches of the small bowel.

In considering the failures of treatment when presumably adequate doses (1.25 g.) were employed, it was observed that the majority were in those with low initial egg counts. This was also observed in the trials with bephenium compounds against hookworm (Goodwin *et al.*, 1958). With low egg counts a difference of a count of one egg is reflected 100 to 200 times in the final count, so that an appreciable error either way is possible; but this is the only practical way of assessment in large-scale work. Wang Cheng-Yi (1959) has suggested a method of culturing the stool whereby the eggs are allowed to hatch and all the larvae are counted. He states that this method is of particular value in avoiding the error that is likely to arise in low counts, that "in counts of $> 5,000/\text{ml}$. the mean value of ova as determined by the two methods (Stoll's and culture) were about the same . . . but as the number of ova decreased $< 5,000/\text{ml}$. then the figures obtained by Stoll's technique and the present method differed quite a bit." He concludes that "when the infestation is heavy the culture method is as good as Stoll's, but when the infestation is light the culture method is much better than Stoll's."

This error in the low counts may therefore be the cause of our apparent failures. It also appears that a few isolated worms are more difficult to eliminate than those which presumably lie massed together. For some reason the drug does not get at them. This possibility also may have accounted for failures in the hookworm series, where those with low counts showed apparently less response to treatment (Goodwin *et al.*, 1958). This was our observation in the present series also. When a dose of 1 g. was used our first real failures in the high

counts occurred. The dose seems to be insufficient to deal with worms even when lying massed together. It therefore confirmed our views that 1.25 g. is the minimum effective dose, as there was a dramatic response to treatment with it.

The only disagreeable side-effect of the drug is vomiting, and that probably owing to its bitter taste. The drug also tends to "repeat."

Most children did not seem to be affected by the worm load itself. They did not feel unwell and so did not welcome the idea of a dose of medicine. In such children and adults the vomiting that occurs is probably largely psychological. For example, we noticed that when one member of a household vomited several others did so soon after; and in well-disciplined groups of children, as in some institutions, vomiting was much less than in others. Again, in the case of hospital in-patients who accepted the drug as part of a normal routine, vomiting was at a minimum.

The incidence of vomiting was highest in those taking the drug as a suspension in water, and much less in those taking it as a freshly prepared suspension in lemon-flavoured syrup. The peppermint-flavoured suspension, when fresh, compared very favourably with that in lemon-flavoured syrup. But after storage for a few weeks it caused a considerable amount of vomiting, though the action of the drug itself was unchanged. This is revealed in Table III. The incidence of vomiting was found to be significantly higher in the peppermint group. The chocolate-coated granules were the best preparation because they caused vomiting in only one out of 19 persons treated. However, their bulk is a disadvantage, for the children tend to swallow the liquid and chew the granules, thus defeating the purpose of the chocolate coating. It is therefore not an acceptable form for the lower age-groups, where the chances of vomiting are greater. It was also observed that in comparable groups taking the drug in lemon-flavoured syrup, almost 100% of the children passed worms, whereas in the group getting chocolate-coated granules, only 9 of the 19 did so. With regard to clearance the results were not significantly different between the two groups, though higher in the group taking the lemon syrup.

The incidence of vomiting is not related to the initial weight of infection. For example, some children with very heavy infections (265,000 eggs per ml.) did not vomit.

We did not observe any laxative effect of the drug, though in children who passed worms there was a frequent desire to pass a stool. This is probably due to the underlying movement of worms. The feeling subsides with the evacuation of worms. We were able to observe this effect better in some other children (not in this series) who were given 1.25 g. of bephenium hydroxynaphthoate twice daily over a period of seven days. Some of them stated that they had two or three "stools" on the first day of treatment, but the "stool" consisted mainly of worms.

We had one case of "shock" (probably from a fall of intra-abdominal pressure) in a 2½-year-old girl with an initial count of 50,000 eggs per ml. of stool. She was not underweight and did not appear undernourished apart from having a somewhat distended abdomen. Bephenium hydroxynaphthoate, 1.25 g., was given at 6.30 a.m., and when we arrived to give her the second dose at 3.30 p.m. we were told that she had passed eight

worms and that she appeared to want to pass a stool all the time. She is said to have passed several coils of worms on the morning of the second day, and by noon appeared to be somewhat listless and cold. She was admitted to hospital for observation and was given a rectal washout and glucose by mouth. She was discharged the same evening and was quite comfortable when seen later that night. She passed a large coil of worms next morning as well.

It was subsequently disclosed that the child had been given a dose of $\frac{1}{2}$ -oz. (15 g.) of piperazine citrate two days earlier, but had not passed worms. The parents had not disclosed this to us as they were anxious to have her treated again because she was in the habit of eating plaster off the wall, which they attributed to worm infection. The symptoms that developed were probably caused by a sudden release of intra-abdominal pressure after evacuation of a large number of worms. The distension that followed was probably due to the loss of tone in a gut that had been chronically distended by large masses of worms. We had earlier had this eventuality in mind in not treating under field conditions another $2\frac{1}{2}$ -year-old child with an egg count of 199,000, but did not expect it in this particular instance. The possibility of this eventuality should be borne in mind when any child passes large numbers of worms after anthelmintic treatment. The dose could not have been too high, for a younger sister, $1\frac{1}{2}$ years old, had the same dose and was unaffected. The child has since had an improved appetite and her general health is reported to be much better.

We had two sisters, aged 8 and $2\frac{1}{2}$ years, who developed wheezing 36 hours after receiving bephenium hydroxynaphthoate. They had 1.25 g. twice on the same day and had passed 25 and 30 worms respectively. They had no previous history of asthma. The elder girl showed a fair amount of distress when seen by us 48 hours after treatment. They both responded well to an injection of aminophylline, were observed for a period of six hours, and subsequently were quite well. Several doctors in charge of out-patient dispensaries have informed us that wheezing and transient fever are often seen in children treated with piperazine citrate for ascariasis. In our experience these were the only allergic manifestations in over 400 children treated with varying doses of bephenium hydroxynaphthoate.

Vague abdominal pain was sometimes complained of by a few children, but in none was it severe enough to cause anxiety.

Summary

Different preparations of bephenium hydroxynaphthoate ("alcopar") in varying doses were given to groups of children, to determine the minimum effective dose for treating ascariasis.

1.25 g. was found to be the minimum dose with optimum results.

The best preparation was a freshly prepared suspension in lemon-flavoured syrup (3.5%).

Vomiting was the only disagreeable side-effect directly attributable to the drug. It was significantly more in children under 4 years of age.

The small dose recommended for treatment of ascariasis could be safely given to any age-group without causing anxiety.

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REFERENCES

- Blagg, W., Schloegel, E. L., Mansour, N. S., and Khalaf, G. I. (1955). *Amer. J. trop. Med. Hyg.*, **4**, 23.
 Goodwin, L. G., Jayewardene, L. G., and Standen, O. D. (1958). *Brit. med. J.*, **2**, 1572.
 Stoll, N. R., and Hausheer, W. C. (1926). *Amer. J. Hyg.*, **6**, March Suppl. p. 80.
 Wang Cheng-Yi (1959). *Clin. med. J.*, **78**, 257.

AORTIC INCOMPETENCE IN ANKYLOSING SPONDYLITIS

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Only recently has it been recognized that patients suffering from ankylosing spondylitis may develop aortic incompetence due to a type of aortitis and aortic endocarditis that has distinctive pathological features. The earliest description of this lesion was given by Mallory *et al.* (1936), but its unique nature and its relationship to joint disease were first recognized by Bauer *et al.* (1951). These workers (Clark *et al.*, 1957) later reported on 22 cases collected over a period of 20 years. Further examples have been recorded by Baker *et al.* (1955), MacMahon *et al.* (1955), Schilder *et al.* (1956), and Toone *et al.* (1959). Ansell *et al.* (1958), giving the first description of the condition in this country, described two cases, with necropsy details of one.

The purpose of this communication is to record the clinical and pathological features of a further case.

Case Report

In 1935 the patient, then a man of 27 with no history of significant previous illness, was passed fit for service in the regular Army. In 1942, at the age of 34, he complained of pain in the back while on a battle course, but continued on full active service as an officer. Three years later he developed painful swelling of the right knee-joint accompanied by pyrexia, followed by pain in other joints and in the back. Radiographs of the spine revealed moderately advanced ankylosing spondylitis.

During the next eight years he continued to serve in the Army, while the joint disease pursued an intermittent progressive course. He received various forms of treatment, including radiotherapy to the spine. In 1949 he had an attack of iritis. In the same year, for the first time in many medical examinations, an apical systolic murmur was noted. This was considered by an experienced physician to be of no pathological significance, and the heart appeared normal on a radiograph of the chest.

In 1954 an exacerbation of spondylitis, with pain in the back, knees, and left shoulder, and with considerable loss of weight, led to his admission to the Queen Alexandra Military Hospital. He was found to have an aortic diastolic murmur, with left ventricular enlargement, collapsing pulse, and high pulse-pressure. There was no evidence of syphilis, and Dr. Evan Bedford thought that the aortic lesion was an example of the aortitis of ankylosing spondylitis.

In 1955 another exacerbation of joint pain and swelling led to his readmission. He now had diminished exercise tolerance and intermittent oedema of the ankles. There was free aortic regurgitation with blowing to-and-fro murmurs in the aortic area, and in addition a low-pitched mitral diastolic murmur. This was thought to be an Austin Flint murmur, as the left auricle was not enlarged.

Thereafter his effort dyspnoea increased rapidly, and in April, 1956, he developed congestive heart failure. The