PHTHALYLSULFATHIAZOLE (SULFATHALIDINE) IN THE TREATMENT OF ENTEROBIASIS (PINWORM INFECTION)

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WITH THE TECHNICAL ASSISTANCE OF VERA DROUGHMAN**

UNTIL recently there has been no laboratory method for selecting compounds for the treatment of human enterobiasis. The parasites will not survive outside the host for long periods, and they cannot be transmitted to laboratory animals.[1] In testing therapeutic agents against two species of mouse pinworm, *Aspicularis tetraptera* and *Syphacia obvelata,* Wells[2, 3, 4] and Chan[5] obtained results of clinical significance. Despite species differences in both host and parasites their studies indicated anthelmintic effects with gentian violet, phenothiazine, oxytetracycline (Terramycin), and bacitracin comparable to those observed in human enterobiasis.

Because Chan's work demonstrated that Sulfathalidine† significantly decreased the number of *Syphacia obvelata* in mice, studies in man with this sulfonamide were undertaken Previous work by Sisk[6] indicated that although this compound, as well as others of the group of poorly absorbed sulfonamides, had anthelmintic activity, they did not completely eliminate *Enterobius vermicularis* in a significant number of patients.

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†Sharp and Dohme's trademark for this drug which has the generic designation "phthalylsulfathiazole." Both Sulfathalidine tablets and a suspension known as Cremothalidine were supplied for this study by the manufacturer.

MATERIALS AND METHODS

Studies were carried out in two institutions, the Children's Heart Hospital and St. Christopher's Hospital for Children. The techniques for the diagnosis of enterobiasis previously described[7] were adapted to the available technical personnel and the character of the patient population.

*Hospitalized Patients.**—The children treated ranged from 4 to 12 years of age. Almost all of them were in the convalescent phase of acute rheumatic fever and were ambulatory. Scotch Tape swabs were obtained by the nursing staff each morning for seven consecutive days from all patients prior to their arising.

The swabs were examined by one of us shortly after their completion. In consultation with the medical director, a decision was then made as to the management of each infected child. Anthelmintic therapy was postponed for children suspected of having active rheumatic fever, because of the possible deleterious effect of sulfonamides on this disease. If eligible for treatment at a later date, these children were re-examined to see if they still harbored helminths. Gentian violet was used for the treatment of individuals suspected of sensitivity to any of the sulfonamide drugs. In patients in whom Sulfathalidine was not contraindicated, therapy with this

*Children's Heart Hospital.

compound was started within a few days of completion of the survey. Treatment was given for one or two weeks. Then after a week of no diagnostic or therapeutic measures, from seven to fourteen post-treatment Scotch Tape swabs were made. As in an earlier study[7] no patient was classified as cured unless he had at least seven negative consecutive post-treatment swabs.

*Ambulatory Clinic Patients.**—Parents seeking help for their children infected with pinworms were referred to one of us in the Medical Clinic. Each mother was taught how to make Scotch Tape swabs and was instructed to make an early morning swab for three consecutive days on each member of the family. On returning the swabs to the clinic, the mothers were given sufficient Sulfathalidine for the prescribed course of treatment and written direction for its administration to all members of the family. Sulfathalidine was not employed for those with a previous history of sensitivity to any medication. In the outpatient group, swabs were made from the eighth through the fourteenth day of the post-treatment phase.

After preliminary experiences indicated that infants and small children had difficulty swallowing Sulfathalidine tablets, a stable and palatable suspension of the drug (Cremothalidine) was employed throughout the rest of the study. When one therapeutic trial failed, the patient was retreated, employing the same or another dosage schedule.

Doses employed were within the ranges recommended by the manufacturer and *New and Nonofficial Remedies*.[8] They were:

*St. Christopher's Hospital for Children.

Sulfathalidine: 0.5 to 4.5 Gm. a day for 7 days.

Under 4 yr.	1 to 2 tab. daily (0.5-1.0 Gm.)
4 to 6 yr.	1 tab. t.i.d. (1.5 Gm.)
6 to 8 yr.	2 tab. b.i.d. (2.0 Gm.)
8 to 13 yr.	2 tab. t.i.d. (3.0 Gm.)
Over 13 yr.	3 tab. t.i.d. (4.5 Gm.)

Sulfathalidine: 2.0 to 6.0 Gm. a day for 7 days.

Under 4 yr.	2 tab. b.i.d. (2.0 Gm.)
4 to 6 yr.	3 tab. b.i.d. (3.0 Gm.)
6 to 8 yr.	4 tab. b.i.d. (4.0 Gm.)
8 to 13 yr.	5 tab. b.i.d. (5.0 Gm.)
Over 13 yr.	4 tab. t.i.d. (6.0 Gm.)

Cremothalidine: 2.0 to 6.0 Gm. a day for 7 or 14 days.

Under 4 yr.	1 tsp. b.i.d. (2.0 Gm.)
4 to 6 yr.	1½ tsp. b.i.d. (3.0 Gm.)
7 to 9 yr.	2 tsp. b.i.d. (4.0 Gm.)
10 to 13 yr.	2½ tsp. b.i.d. (5.0 Gm.)
Over 13 yr.	3 tsp. b.i.d. (6.0 Gm.)

Cremothalidine: 1.0 to 8.0 Gm. a day for 7 days.

Under 1 yr.	½ tsp. b.i.d. (1.0 Gm.)
1 to 4 yr.	1 tsp. b.i.d. (2.0 Gm.)
4 to 6 yr.	2 tsp. b.i.d. (4.0 Gm.)
7 to 9 yr.	2½ tsp. b.i.d. (5.0 Gm.)
10 to 13 yr.	3 tsp. b.i.d. (6.0 Gm.)
Over 13 yr.	4 tsp. b.i.d. (8.0 Gm.)

Gentian violet was administered in the form of four-hour enteric-coated tablets in divided doses after meals. The doses were the same as those previously tried.[7]

Gentian violet: 0.02 to 0.18 Gm. a day for 7 days.

Under 4 yr.	1 or 2 small tab. (0.02 Gm.)
4 to 6 yr.	3 small tab. (0.03 Gm.)
6 to 8 yr.	6 small tab. (0.06 Gm.)
8 to 13 yr.	3 large tab. (0.09 Gm.)
Over 13 yr.	6 large tab. (0.18 Gm.)

RESULTS

Children's Heart Hospital.—Because of possible rheumatic fever in several children and later because of an epidemic of mumps, treatment was deferred in eight infected children. Of these, three had at least seven negative swabs after a period of hypothetical "treatment."

Gentian violet was very effective, apparently ridding six children of worms without any therapeutic failures, even though three of this group vomited repeatedly during the course of therapy.

Small doses of Sufathalidine, 0.5 to 4.5 Gm. a day, produced poor results with only two cures in a group of seven children. No toxic reactions were observed.

Trials with daily doses of 2 to 6 Gm. of Cremothalidine for fourteen days were more effective, curing twenty-three of twenty-nine children. This result was significantly better than in the control groups. On the tenth day of treatment one child had six of sixteen patients without any untoward reactions.

Two to 6 Gm. a day for one week cured five of eleven persons with two possible instances of toxicity. During very hot weather the mother of a large family reported that two children had subaxillary rashes. These children unfortunately were not seen by a physician at the time and it was not determined whether the rashes

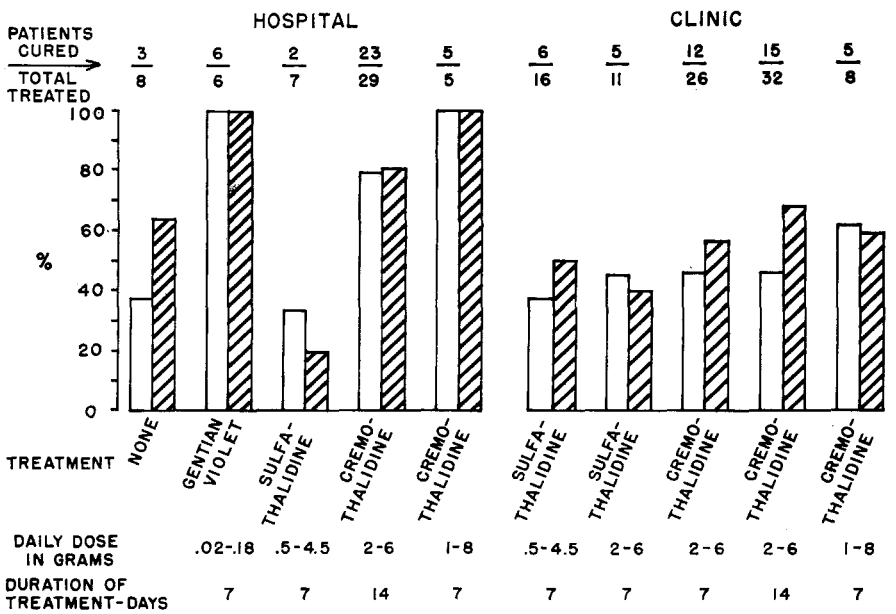

Fig. 1.—Effects of various regiments on cure rates (white bars) and change in incidence of ova-bearing slides (shaded bars).

urticaria which subsided promptly on cessation of therapy.

All of the five children treated for one week with 1 to 8 Gm. of Cremothalidine a day were cured without any evidence of toxicity. In comparison with the outcome of infection in the untreated group, this result is probably significant.

St. Christopher's Hospital for Children.—Sulfathalidine in daily doses of 0.5 to 4.5 Gm. for seven days cured represented miliaria or reactions to the medication.

Cremothalidine in daily doses of 2 to 6 Gm. was given for one week. Of twenty-six patients so treated, twelve were cured. When the same doses were administered for two weeks the results were no better, there being fifteen cures on thirty-two therapeutic trials. With a daily dose of 1 to 8 Gm. a day for one week

five out of eight persons were cured.

In hospital and clinic studies the incidence of ova-bearing slides was reduced after treatment (see Table I and Fig. 1).

DISCUSSION

Since apparent spontaneous cases can occur, the observation of an untreated group is advisable to prevent unwarranted enthusiasm about the anthelminthic potency of any drug.

Our primary responsibility in both institutions was the eradication of the parasites and we felt justified in withholding treatment in only eight hospitalized children because of definite contraindications. In keeping with the criteria established for successful therapy, three of them became spontaneously "cured" after a period of hypothetical treatment. On one child's seven "pretreatment" slides

TABLE I. THERAPEUTIC EFFECTIVENESS AND TOXICITY OF GENTIAN VIOLET, SULFATHALIDINE, AND CREMOTHALIDINE

TREATMENT	NO. PATIENTS	NO. CURED	TOXICITY	SCOTCH TAPE SLIDES		
				PRETREATMENT POSITIVE/ TOTAL	POST-TREATMENT POSITIVE/ TOTAL	DECREASE PER CENT POSITIVE SLIDES
Hospital						
None	8	3 (38%)	-	20/56 (36%)	10/77 (13%)	64
Gentian violet 0.02-0.18 Gm. a day for 7 days	6	6 (100%)	3 patients vomited	14/42 (33%)	0/64	100
Sulfathalidine 0.5-4.5 Gm. a day for 7 days	7	2 (29%)	0	22/49 (45%)	35/98 (36%)	20
Cremothalidine 2-6 Gm. a day for 14 days	29	23 (79%)	1 patient had urticaria	132/229 (58%)	22/209 (11%)	81
Cremothalidine 1-8 Gm. a day for 7 days	5	5 (100%)	0	13/35 (37%)	0/35	100
Clinic						
Sulfathalidine 0.5-4.5 Gm. a day for 7 days	16	6 (38%)	0	43/58 (74%)	42/115 (37%)	50
Sulfathalidine 2-6 Gm. a day for 7 days	11	5 (45%)	2 patients had rashes	20/48 (42%)	19/77 (25%)	40
Cremothalidine 2-6 Gm. a day for 7 days	26	12 (46%)	0	57/88 (65%)	51/182 (28%)	57
Cremothalidine 2-6 Gm. a day for 14 days	32	15 (47%)	0	88/116 (76%)	57/233 (24%)	68
Cremothalidine 1-8 Gm. a day for 7 days	8	5 (63%)	1 patient had abdominal cramps	26/30 (87%)	25/70 (36%)	59

only one egg was found, another had ova on only one slide, but the third had four positive slides.

According to Jung and Beaver,[9] a low incidence of pretreatment positive slides is related to a high cure rate. This might account for the apparently better results in the hospital group where more children with a low incidence of ova-bearing slides were treated (see Table II). The number of patients in each group were too small for verification by statistical analysis.

negligible systemic toxicity. That this compound largely remains in the gastrointestinal tract is ideal for the treatment of enterobiasis, since the parasite's habitat is limited to the cecum, appendix, and colon.

Since infection with pinworms is a family problem, making treatment of all members of the family advisable, and since enterbiasis does not threaten life and frequently produces no symptoms, the use of expensive medication is rarely justified. Certain antibiotics such as oxytetracy-

TABLE II. EFFECTS OF THERAPY ON PATIENTS WITH VARYING INCIDENCE OF PRETREATMENT OVA-BEARING SLIDES
CREMOTHALIDINE, 2 TO 6 GM. DAILY FOR FOURTEEN DAYS

HOSPITAL			CLINIC		
INCIDENCE OF OVA-BEARING SLIDES BEFORE TREATMENT* (%)	NUMBER OF PATIENTS	NUMBER CURED	INCIDENCE OF OVA-BEARING SLIDES BEFORE TREATMENT† (%)	NUMBER OF PATIENTS	NUMBER CURED
100	6	2 (33%)	100	10	3 (30%)
86	3	3 (100%)	75	1	0
71	4	4 (100%)	67	4	2 (50%)
57	3	2 (67%)	57	1	0
36	2	2 (100%)	50	2	1 (50%)
29	4	3 (75%)	33	7	6 (86%)
25	1	1 (100%)	14	1	0
14	5	5 (100%)			

*Only patients with at least seven pretreatment slides are included.
†Only patients with at least three pretreatment slides are included.

Although Cremothalidine is a weaker anthelminthic than gentian violet, nurses and mothers agreed that Cremothalidine was much easier to administer to infants and small children who had difficulty in swallowing enteric-coated gentian violet tablets. Those who had had previous experience with the gastrointestinal irritation and the vomiting of purple material from the use of gentian violet appreciated the lack of such reactions accompanying treatment with Cremothalidine.

The poor absorption of Sulfathalidine from the gastrointestinal tract accounts in large measure for the

cline (Terramycin)[10] and bacitracin[11] are clinically effective but the necessity of treating family groups demands the consideration of economic aspects of therapy. Synergism between antibiotics and poorly absorbed sulfonamides demonstrated in mice by Chan[5] suggests that Cremothalidine in combination with an antibiotic by reducing the amount of antibiotic required may result in an effective and less expensive medication.

CONCLUSIONS

1. Daily doses of Cremothalidine from 2 to 6 Gm. given for two weeks cured twenty-three (79 per cent) of

twenty-nine children in a children's hospital, and fifteen (47 per cent) of thirty-two in a clinic population of all ages. One to 8 Gm. a day given for one week cured all five children in the hospital group, and five of eight (63 per cent) in the dispensary.

2. Although not as potent an anthelmintic as gentian violet, Cremothalidine did not produce the gastrointestinal irritation associated with the dye, and because of its palatable liquid form was much easier to administer to infants and small children.

Note: Since the preparation of this paper, tablets each containing 0.2 Gm. of neomycin and 0.3 Gm. of Sulfathalidine have been tried. Three to ten tablets given twice a day for seven days cured nine children with no treatment failures. Because fifteen of twenty-three individuals treated complained of anorexia, nausea, or vomiting, the effectiveness of smaller doses should be studied.

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