

## PHTHALYLSULFATHIAZOLE IN THE TREATMENT OF DIARRHEA IN CHILDREN

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THE treatment of acute microbial diarrhea during infancy and childhood has become more satisfactory since the sulfonamides have been used as adjuvants to a limited bland diet and adequate parenteral and oral fluids. The periods of acute illness and of convalescence have been shortened, mortality rate lowered, and "days in the hospital" reduced. Stool cultures have become negative sooner, resulting in earlier release from isolation technique and quarantine. The early *in vivo* disinfection of the stool results in a saving of hospital quarantine days, and it eliminated carriers, recurrences, and secondary contact cases.

Although chemically similar, two types of sulfonamides with different physical and pharmacodynamic characteristics have been synthesized and used successfully in the treatment of children with diarrhea. One is very soluble, is absorbed quickly, and is circulated in the blood in a high concentration. The other is only slightly soluble, is absorbed poorly, and produces a low blood but high intestinal concentration. The successful response to the drugs with paradoxical physical characteristics has stimulated the synthesis and clinical investigation of new compounds of both types.

In 1941, Poth and Knotts<sup>4</sup> reported excellent results with succinylsulfathiazole as an intestinal antiseptic, and in 1943 Poth and Ross<sup>2</sup> introduced phthalylsulfathiazole. Their investigation showed the latter sulfonamide to be four times as effective as succinylsulfathiazole as a gastrointestinal bacteriostatic. Their tests were made on dogs. Coliform colonies obtained from the feces of the experimental animals were used as indicators. They demonstrated that the drug was sparingly absorbed and that it had extremely low toxicity. The low toxicity was further demonstrated by Mattis and associates.<sup>1</sup> They gave doses of 10 Gm. per kilogram to white mice and 5 Gm. per kilogram per day for thirty days to monkeys without toxic effect.

Based on the favorable reports, a therapeutic evaluation of phthalylsulfathiazole as an intestinal antiseptic was undertaken. During the summer and fall of 1943, 121 patients entered the Children's Division of Cook County Hospital with a history of abnormally frequent and liquid stools during the preceding few hours. Following admission, a diagnosis of diarrhea was established in ninety-eight of these (Group A).

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\*Deceased.

In the remaining twenty-three, the number of stools passed within the first twenty-four hours after admission was less than three, and these children are grouped separately (Group B). Fifty-seven other children admitted to the hospital with complaints not associated with the gastrointestinal tract (Group C), had stool examinations for comparison with the other groups.

Of Group A, twenty-five were treated with phthalylsulfathiazole, twenty-nine with sulfathiazole, ten with kaopectate, and two, diagnosed as typhoid fever, with sulfaguanidine, respectively. The thirty-two others of this group were treated with various combinations of these drugs. Forty-six of the patients in Group A were under, and fifty-two were over 12 months of age. Three deaths occurred, all in children under 12 months of age. (Table I). Of Group B, six were treated with phthalylsulfathiazole, thirteen with sulfathiazole, one with kaopectate, and three with combinations of these drugs. (Table II.)

Bacteriologic cultures of 291 stools obtained from the ninety-eight children with diarrhea (Group A) were studied. Two typhoid fever patients were included in this group although neither of these had diarrhea. Forty-four stools of twenty-three other patients (Group B) with an admission complaint of frequent evacuations were examined. These patients were grouped separately and not included in the diarrheal series because they did not meet the requirements of our definition of diarrhea, that is three or more stools during the first twenty-four hours after admission. The stools of the fifty-seven children in group C with symptoms unrelated to the gastrointestinal tract, were examined to determine the incidence of recognized diarrhea producing organisms in nondiarrheal stools in the hospital population.

From the stools of eighteen (20 per cent) of the children in Group A, *Shigella dysenteriae* or *paradysenteriae* was cultured in twenty-six instances, *Eberthella typhosa* in two (2 per cent) instances, and *Salmonella paratyphi* (*Salmonella manhattan*) in one instance (1 per cent). *S. dysenteriae* was cultured in seven instances in six (25 per cent) of the patients in Group B. No dysentery pathogens were recovered from the stools of the fifty-seven patients in Group C. *Proteus morgani* was cultured from the stools of seven (7 per cent) of the ninety-eight children in the diarrheal group, from four (16 per cent) of the twenty-three in Group B and from three (5 per cent) of those in Group C.

Because of the difference in prognosis, the children with diarrhea (Group A) have been divided into two subgroups. The first includes those under, and the second those over, 12 months of age.

The incidence of severity of the disease and the response to specific drugs is shown, together with the bacteriologic findings in the feces of each of these subgroups. (Tables III and IV.)

The sulfonamides studied were given in divided doses of at least one grain per pound of body weight in twenty-four hours. The results of 126 determinations for the sulfonamide content of the blood are shown in Table V. There were thirty-five sulfonamide blood level determinations on patients receiving phthalylsulfathiazole; twenty-nine of these were less than one milligram in 100

TABLE I. THERAPY, AGE DISTRIBUTION, AND RESULTS

TYPE OF MEDICATION	AGE DISTRIBUTION				RESULTS			
	UNDER 12 MONTHS		OVER 12 MONTHS		TOTALS		RECOV- ERED	DEATHS
	NO. CASES	AV. DAYS OF DIAR- RHEA AFTER MEDI- CATION	NO. CASES	AV. DAYS OF DIAR- RHEA AFTER MEDI- CATION	NO. CASES	AV. DAYS OF DIAR- RHEA AFTER MEDI- CATION		
Phthalylsulfathiazole	8	5.9	17	2.5	25	3.6	25	0
Phthalylsulfathiazole and sulfathiazole	3	4.6	1	1.9	4	3.8	3	1
Phthalylsulfathiazole and kaopectate	1	16.0	7	4.6	8	6.0	8	0
Phthalylsulfathiazole and kaopectate sulfathia- zole	3	11.3	0	0	3	11.3	1	2
Phthalylsulfathiazole and kaopectate sulfamer- azine	0	0	1	5.0	1	5.0	1	0
Total	15	7.7	26	3.1	41	4.6	38	3
Sulfathiazole	14	3.9	15	1.7	29	2.7	29	0
Sulfathiazole and kaopectate	8	6.4	1	1.0	9	5.8	9	0
Sulfathiazole and sulfamerazine	1	6.0	0	0	1	6.0	1	0
Sulfathiazole and kaopec- tate and nipectin	2	7.5	0	0	2	7.5	2	0
Sulfathiazole and nipectin	1	4.0	0	0	1	4.0	1	0
Total	26	5.0	16	1.6	42	3.7	42	0
Kaopectate	2	8.0	8	4.0	10	4.8	10	0
Kaopectate and nipectin	2	6.0	0	0	2	6.0	2	0
Kaopectate and Sulfamerazine	1	4.0	0	0	1	4.0	1	0
Total	5	6.4	8	4.0	13	4.9	13	0
Sulfaguanadine	0	0	2	0	2	0	2	0
Totals	46	—	52	—	98	—	95	3

TABLE II. THERAPY AND AGE DISTRIBUTION OF THE CASES IN GROUP B

TYPE OF MEDICATION	AGE DISTRIBUTION						TOTALS
	UNDER 12 MONTHS			OVER 12 MONTHS			
	NON- SPECIFIC	SPECIFIC	TOTALS	NON- SPECIFIC	SPECIFIC	TOTALS	
Phthalylsulfathiazole	1	0	1	3	2	5	6
Phthalylsulfathiazole and sulfathiazole	0	0	0	1	0	1	1
Phthalylsulfathiazole and kaopectate	0	0	0	1	0	1	1
Total	1	0	1	5	2	7	8
Sulfathiazole	5	0	5	4	4	8	13
Sulfathiazole and kaopectate	0	0	0	1	0	1	1
Total	5	0	5	5	4	9	14
Kaopectate	0	0	0	1	0	1	1
Total	0	0	0	1	0	1	1
Totals	6	0	6	11	6	17	23

TABLE III. CORRELATION OF SEVERITY OF DIARRHEA, BACTERIOLOGY, AND RESPONSE TO MEDICATION IN CHILDREN UNDER TWELVE MONTHS OF AGE

MEDICATION		BACTERIOLOGY				RESULTS			
TYPE	SEVERITY	NONSPECIFIC		DYSENTERY		TOTAL NO. CASES	AVERAGE DAYS DIARRHEA AFTER MEDICATION	RECOVERED	DEATHS
		NO. CASES	AVERAGE DAYS DIARRHEA AFTER MEDICATION	NO. CASES	AVERAGE DAYS DIARRHEA AFTER MEDICATION				
Phthalylsulfathiazole									
	Severe	1	6.0	0	0	1	6.0	1	0
	Moderate	5	6.4	0	0	5	6.4	5	0
	Mild	2	4.5	0	0	2	4.5	2	0
Total		8	5.9	0	0	8	5.9	8	0
Kaopectate									
	Severe	0	0	0	0	0	0	0	0
	Moderate	1	12.0	0	0	1	12.0	1	0
	Mild	1	4.0	0	0	1	4.0	1	0
Total		2	7.0	0	0	2	7.0	2	0
Sulfathiazole									
	Severe	1	10.0	0	0	1	10.0	1	0
	Moderate	6	3.6	0	0	6	3.6	6	0
	Mild	7	3.1	0	0	7	3.1	7	0
Total		14	3.8	0	0	14	3.8	14	0
Combinations									
	Severe	(+2	15.5	0	0	+2	15.5	0	2)
		2	7.5	0	0	2	7.5	2	0
		(++1	2.0	0	0	++1	2.0	0	1)
	Moderate	11	7.4	0	0	11	7.4	11	0
	Mild	5	4.4	1	5.0	6	4.5	6	0
Total		(+,++3	11.0	0	0	+,++3	11.0	0	3)
		18	6.6	1	5.0	19	6.4	19	0

+, two deaths with persistence of diarrhea for twenty and eleven days, respectively.

++, one death with persistence of diarrhea for two days.

c.c. of blood (usually reported as "none" or a "trace"). The remaining six levels ranged from 1 to 4 mg. Of the thirty-two sulfonamide determinations on children receiving sulfathiazole, seven were less than one milligram, four between one and 2, eight between 2 and 3, five between 3 and 4 and six between 4 and 5 mg. per cent. The remaining two blood levels were over 5 mg. Fifty-nine determinations were made on the blood of children receiving combinations of sulfonamides. They ranged from 0 to 7 and 8 mg. per cent. No child manifested any symptoms suggestive of a toxic reaction to any of the sulfonamides.

Diarrhea was classified from the number of stools during the first twenty-four hours after admission as mild if more than three but less than five, moderate if five to seven, severe if there were seven or more stools in twenty-four hours. When a patient of the diarrheal series passed fewer than three stools in twenty-four hours, he was classified as "recovered." In all instances, the first stool after admission was cultured, and drug therapy instituted immediately thereafter without awaiting the bacteriologic results. The efficacy of the treatment was estimated from the number of days diarrhea persisted after the institution of the specific drug.

The twenty-five diarrheal patients receiving phthalylsulfathiazole alone (Table I) recovered after an average of 3.6 days of medication. The sixteen re-

TABLE IV. CORRELATION OF SEVERITY OF DIARRHEA, BACTERIOLOGY, AND RESPONSE TO MEDICATION IN CHILDREN OVER TWELVE MONTHS OF AGE

MEDICATION		BACTERIOLOGY				RESULTS			
TYPE	SEVERITY	NONSPECIFIC		DYSENTERY		TOTALS		RECOV- ERED	DEATHS
		NO. CASES	AV. DAYS DIARRHEA AFTER MEDI- CATION	NO. CASES	AV. DAYS DIARRHEA AFTER MEDI- CATION	NO. CASES	AV. DAYS DIARRHEA AFTER MEDI- CATION		
Phthalylsul- fathiazole	Severe	2	2.5	4	3.5	6	3.2	6	0
	Moderate	2	2.5	0	0	2	2.5	2	0
	Mild	5	1.4	4	2.7	9	2.0	9	0
Total		9	1.9	8	3.1	17	2.5	17	0
Kaopectate	Severe	0	0	0	0	0	0	0	0
	Moderate	2	4.0	1	9.0	3	5.7	3	0
	Mild	3	3.3	2	2.5	5	3.0	5	0
Total		5	3.5	3	4.6	8	4.0	8	0
Sulfathiazole	Severe	2	2.0	1	2.0	3	2.0	3	0
	Moderate	3	2.0	0	0	3	2.0	3	0
	Mild	6	1.5	3	1.3	9	1.4	9	0
Total		11	1.8	4	1.5	15	1.6	15	0
Combinations	Severe	0	0	0	0	0	0	0	0
	Moderate	3	6.3	1	10.0	4	7.2	4	0
	Mild	5	1.8	1	1.0	6	1.7	6	0
		8	3.5	2	5.5	10	3.9	10	0

TABLE V. SULFONAMIDE BLOOD LEVELS OBTAINED WITH SULFATHIAZOLE AND COMBINATIONS OF THESE TWO DRUGS

THERAPY	BLOOD LEVELS IN MG. %								TOTALS
	0-1%	1-2%	2-3%	3-4%	4-5%	5-6%	6-7%	7-8%	
No. determinations for									
Phthalylsulfathiazole	29	2	1	3	0	0	0	0	35
Sulfathiazole	7	4	8	5	6	2	0	0	32
Combination of sulfonamides	36	7	3	7	3	1	1	1	59
Totals	72	13	12	15	9	3	1	1	126

ceiving this drug in combination with sulfathiazole, kaopectate, and/or sulfamerazine required an average of 6.7 days for cure. The twenty-nine patients receiving sulfathiazole alone recovered in 2.7 days. The use of sulfathiazole with kaopectate, sulfamerazine, and/or nipectin in thirteen cases was followed by recovery after an average of 6.7 days. In ten patients given kaopectate only, recovery followed in an average of 4.8 days. Two children given a combination of kaopectate and nipectin recovered in six days. Kaopectate and sulfamerazine used together in one case was followed by the reduction of the number of stools to normal in 4 days.

There were forty-six infants in the subgroup of diarrheal cases under 12 months of age (Table III). Eight of these receiving phthalylsulfathiazole alone recovered in an average of 5.8 days. The fourteen treated with sulfathiazole alone recovered in 3.8 days. Kaopectate alone given to two cases was followed by reduction of the number of stools to normal in 7 days. In

twenty-two cases, the use of combinations of the three medicaments was followed by death in three instances and by recovery in nineteen in an average of 6.4 days.

The three children that died received phthalylsulfathiazole and sulfathiazole and two received kaopectate in addition. The postmortem examination of these three infants revealed marked cachexia and malnutrition. Nonspecific enteritis was found in two; in one it was complicated by aspiration bronchopneumonia, and in another by an old peritonitis with firm adhesions to the gall bladder. Associated with the peritonitis was mesenteric glandular hyperplasia.

The treatment of the three children who died included in all instances a period of marked restriction of oral intake of food, intravenous plasma, blood, and saline or Hartman's solution infusions. Phthalylsulfathiazole and sulfathiazole were given to the three infants in doses of one grain to 3 grains per pound body weight in twenty-four hours for the entire duration of their hospital stay, which ranged from two to twenty days. Kaopectate was given to two, as was parenteral Vitamin B. In one instance, sulfathiazole was given as the sodium salt, intravenously. There were eight determinations for sulfonamide content in the blood; all were reported as "trace" or "none."

In the subgroup of diarrheal patients over 12 months of age, there were fifty children (Table IV). (The two cases of typhoid fever are not included.) Of these, seventeen were treated with phthalylsulfathiazole alone; they recovered after an average of 2.5 days. The fifteen patients treated with sulfathiazole recovered after an average of 1.6 days. The eight receiving kaopectate required 4 days before they could be considered "cured." Ten patients receiving a combination of medicaments had a persistence of diarrhea for 3.9 days. The two typhoid fever patients were treated with sulfaguanidine although they had no diarrhea.

From the stools of nineteen of the ninety-eight patients with diarrhea (Group A), organisms commonly accepted as active etiologic factors in dysentery were obtained one or more times. Repeated examinations of stools in the other seventy-seven patients were negative. Only one positive culture occurred in the subgroup under 12 months of age; the other forty-five infants had negative stool cultures. Eighteen positive cultures were obtained from patients over 12 months of age; the stools of the remaining thirty-four were negative. Of the older children given phthalylsulfathiazole alone (Group A), nine were nonspecific and eight with specific diarrheas recovered in 1.9 and 3.1 days respectively. Eleven of the older children (Group A) with nonspecific and four with specific diarrhea, given sulfathiazole alone, recovered in 1.8 and 1.5 days, respectively. The use of kaopectate was followed by a reduction of the number of stools to normal in 3.6 days in five nonspecific and 4.6 days in three specific cases of diarrhea. The combination of the above drugs was followed by recovery in 3.5 days for the two specific cases of diarrhea. It is to be noted that there were no deaths in the subgroup of children over 12 months of age.

Twenty-three children (Group B) admitted because of a complaint of diarrhea were grouped separately because they did not conform to our definition of diarrhea (Table II). Six of these were under and seventeen over 12 months of age. Bacteriologic examination of forty-four stools from these patients resulted in the identification of *S. dysenteriae* in the feces of six patients (13 per cent), all over 12 months of age. This group of children was treated with the same medicament as the diarrheal group, but because of the absence of diarrhea, no statistical inferences as to their efficacy is drawn. No toxic effects were noted.

#### RESULTS

It will be seen from Table I that the response to all of the drugs apparently was more favorable in the group over 12 months of age than in those under, and that the response to sulfathiazole and its combinations apparently was more favorable in both age groups than was the response to phthalylsulfathiazole and its combinations and kaopectate and its combinations.

Table III is an analysis of the incidence of specific and nonspecific diarrheas in the group under 12 months of age. Three deaths occurred in this group in infants from whose feces specific organisms were *not* recovered. There was but one instance in which specific organisms causing diarrhea were recovered from the feces of the infants under 12 months of age. The response to the various drugs investigated showed a trend in favor of sulfathiazole and a superiority of phthalylsulfathiazole over kaopectate.

From Table IV, which is the analysis of the diarrheal group over 12 months of age, it would seem that there is a trend in favor of sulfathiazole. The recoveries on this drug occurred in 1.6 days as compared with 2.5 on phthalylsulfathiazole and 4 on kaopectate. Sulfathiazole seems to have been more effective both in the specific and nonspecific diarrheas in this age group when compared with phthalylsulfathiazole or kaopectate. Phthalylsulfathiazole seemed more effective in the specific than in the nonspecific diarrheas.

In Table V is shown the results of 126 determinations of sulfonamide blood content. Very little phthalylsulfathiazole was absorbed in comparison with the absorption of sulfathiazole. Since there were no toxic symptoms in any of the cases, this has only academic significance.

A statistical analysis of the results following the use of phthalylsulfathiazole, sulfathiazole, and kaopectate, and their combinations in the treatment of diarrhea in the two groups of children, one under and the other over 12 months of age, reveals the following:

In an over-all statistical analysis, including all children in Group A, *no significant difference\** was noted in the effects of any of the three drugs, phthalylsulfathiazole, sulfathiazole, and kaopectate.

A specific comparison was made of phthalylsulfathiazole alone and in combination with sulfathiazole and with kaopectate, and sulfathiazole alone was compared with its combinations with other drugs. A significant difference

\*A difference was considered significant if it reached "the 5 per cent level of significance." This means that the chances are 1 in 20 that a difference as large as this could be obtained through errors of random sampling.

was found to exist in the results following the administration of the single drug when compared to its use in combinations. The multiple drugs did not produce as favorable results as followed the use of a single drug.

In all the statistical analyses made, a significant difference was found to exist in the response to treatment of the two age groups (one under and the other over 12 months of age). The drugs, whether administered singly or in combination, were more effective on the older age group.

#### SUMMARY

1. There was no statistically significant difference in the results obtained following the administration of phthalylsulfathiazole in comparison with the results following the use of sulfathiazole in the treatment of diarrheas in the children at Cook County Hospital during 1943.

2. Combinations of phthalylsulfathiazole, or of sulfathiazole, with other drugs appeared to be less effective than the use of individual drugs.

3. Both phthalylsulfathiazole and sulfathiazole were more effective in the treatment of diarrheas in the children over 12 month of age than in those under that age

4. Although statistically not evident, sulfathiazole appeared to shorten the course of diarrhea, whether due to specific or nonspecific organisms, more than phthalylsulfathiazole in all age groups.

5. The trend of response in children with diarrheas due to specific organisms was more favorable following the administration of sulfathiazole than following phthalylsulfathiazole.

6. Sulfathiazole appeared to be more effective in the treatment of diarrheas due to specific organisms than it was in the treatment of the nonspecific cases. The difference, however, is not statistically significant.

7. No toxic symptoms were observed as a result of the use of any of these drugs.

8. The post-mortem findings of the three infants that expired showed no evidence of any ill effect from drug therapy.

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\*This is statistically true, but patients receiving multiple drugs were not random samples. They were given more than one drug because of failure to respond to the initial medication.