

THE USE OF PHTHALYLSULFATHIAZOLE (SULFATHALIDINE) IN COLONIC SURGERY*

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IN 1941, Poth and Knotts¹ introduced succinylsulfathiazole (sulfasuxidine) as an intestinal antiseptic and bacteriostatic agent. It has proved especially valuable as an adjunct to surgery of the large bowel, as well as in the treatment of certain medical conditions. A further improvement was made in this field with the discovery of phthalylsulfathiazole (sulfathalidine§) by Poth and Ross² in 1943. This new drug has the advantage of having twice the bacteriostatic activity of succinylsulfathiazole but requiring only half to one third of its dosage. In addition, the drug has not given rise to any toxic reactions such as have occasionally been seen with succinylsulfathiazole. Mattis et al.,³ in extensive toxicologic studies on the effect of phthalylsulfathiazole in mice, rats and monkeys, reported no toxic manifestations in spite of large doses administered orally every four hours for thirty days. They found extremely low blood concentrations of free and total sulfathiazole, which they attributed to retention in the gastrointestinal tract of all but small amounts of the drug; the small amount that was absorbed was rapidly excreted by the kidneys. Our studies of the blood and urine concentrations of this drug are in agreement with the findings of these investigators. Furthermore, phthalylsulfathiazole is effective in the presence of diarrhea or in patients who are receiving purgatives, whereas the effectiveness of succinylsulfathiazole under these conditions is greatly reduced.

The stools following the use of phthalylsulfathiazole are solid and retain some of their odor, as opposed to the odorless, semifluid movements that occur after the giving of succinylsulfathiazole. The exact mode of action of these drugs is not yet clearly understood. The chemical and bacteriostatic properties of phthalylsulfathiazole have been studied and reported by Poth and Ross.⁴

In this paper we are reporting our experience with the new drug at the Pondville Hospital, where it has been used in connection with surgery of the large bowel. It has been employed in the preoperative preparation of 51 unselected cases over a period of fifteen months. It has also been used in 12 cases of nonspecific gastroenteritis with diarrhea, in which it has apparently been of definite benefit. Our studies of the blood and urine concentrations of this

drug are in agreement with the findings of the above investigators.

The type of case in which phthalylsulfathiazole was used is shown in Table 1. In several of the cases the drug was used more than once, when the operation was done in stages. There was no evidence in any case of sensitivity to the preparation.

In Table 2 are shown the types of operation performed. There were 3 cases in the group given

TABLE 1. Cases in Which Phthalylsulfathiazole Was Employed.

DIAGNOSIS	No. OF CASES
Carcinoma of rectum	30
Carcinoma of left colon and rectosigmoid	13
Carcinoma of right colon	4
Carcinoma of transverse colon	1
Tumor of rectovaginal septum	1
Polyposis of large bowel	1
Carcinoma of urinary bladder	1
Total	51

routine preoperative doses of phthalylsulfathiazole in which the patients subsequently refused operation or in which it was considered inadvisable. The administration of the drug was stopped on the morning of operation and was not continued postoperatively in all cases except 1, in which a tumor of the rectovaginal septum was removed. The rectum was opened and repaired during operation, and it was decided to continue the drug. Convalescence was uncomplicated.

In cases of resection of a blind loop of bowel or second-stage posterior excision of the rectum, daily preoperative irrigations with a suspension of

TABLE 2. Types of Operation Performed.

OPERATION	No. OF CASES
Abdominoperineal resection:	
One-stage	12
Two-stage	2
Resection of tumor, transverse and descending colon and rectosigmoid, with primary anastomosis	9
Palliative colostomy	9
Colostomy revision	5
Right colectomy:	
One-stage	3
Two-stage	1
Colostomy or enterostomy closure	2
Ureterointestinal anastomoses	2
Resection of blind loop of bowel	2
Enterenterostomy	1
Excision of tumor of rectovaginal septum	1
Total	49

phthalylsulfathiazole were given. Of the 9 patients who received resection of tumors of the transverse, descending or rectosigmoid colon, 4 had a preliminary or complementary cecostomy, 4 had Miller-Abbott tube decompression, and 1 had neither. In none of these cases was there any serious postoperative distention.

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Dosage and Preoperative Preparation

The routine procedure has been to place these patients on a low-residue diet and to begin the administration of phthalylsulfathiazole five or six days before operation. Giving the drug for shorter periods of time preoperatively proved unsatisfactory. It has, however, been given in full dosage for as long as fourteen days without any ill effect. The initial dose is 0.05 gm. per kilogram of body weight, or between 2.5 and 4.5 gm. for most patients. Following this, 1 gm. (two tablets) is given every four hours day and night. Enemas are used preoperatively when indicated; strong purgatives are not employed. Whole blood, plasma and amino acid preparations are used as indicated in the correction of anemia and low serum protein. For twenty-four hours be-

Laboratory Data

Determinations of the blood and urine levels of phthalylsulfathiazole were made daily, as well as red-cell counts, white-cell counts and hemoglobin determinations, in the 19 cases listed in Table 3. No facilities were available for bacteriologic examination of the stools. Such studies have, however, been reported by Poth and Ross,⁵ and the effectiveness of phthalylsulfathiazole in reducing coliform and other organisms has been well established.

In Table 3, it will be noted that the daily dose as well as the number of doses varied; this was due to the fact that in these cases an attempt was made to adjust the dosage as accurately as possible to the patient's weight. In view, however, of the extremely

TABLE 3. *Blood and Urine Concentrations of Phthalylsulfathiazole as Sulfathiazole.*

CASE NO.	DAILY DOSE gm.	NO. OF DOSES DAILY	AVERAGE BLOOD CONCENTRATION		AVERAGE URINE CONCENTRATION	
			FREE mg./100 cc.	CONJUGATED mg./100 cc.	FREE mg./100 cc.	CONJUGATED mg./100 cc.
1	4.5	6	0.13	0.54	8.8	31.1
2	3.0	6	6.31	0.17	1.2	1.9
3	2.5	5	0.04	0.28	2.5	4.6
4	2.5	5	0.24	0.40	3.5	10.0
5	3.0	6	0.23	0.59	10.7	17.5
6	3.0	6	0.15	0.31	2.3	6.0
7	3.0	6	0.28	0.41	1.5	4.0
8	3.0	6	2.04	2.22	5.8	12.9
9	3.0	6	0.08	0.60	3.6	7.1
10	2.5	5	0.09	0.20	1.4	2.9
11	3.0	6	0.13	0.31	3.9	11.0
12	4.0	4	0.08	0.18	5.2	13.9
13	3.0	6	0.68	0.81	11.9	32.6
14	3.0	6	2.68	14.14	19.6	36.8
15	2.5	5	0.14	0.26	2.9	8.6
16	3.5	6	0.19	0.20	14.1	26.9
17	3.0	6	0.24	0.41	3.6	12.8
18	2.5	5	0.52	0.78	8.4	21.6
19	3.0	6	0.18	0.58	12.3	36.6

fore surgery the patient is given only clear liquids by mouth, and routine doses of sulfadiazine are administered during this period, either by mouth or intravenously.

At the time of operation, in all cases except 1 in which there was no obstruction, the bowel was found to be well cleaned out and free from distention. The exception was a case of unobstructed carcinoma of the rectum in which abdominoperineal resection was carried out after the patient had received phthalylsulfathiazole for only three days. In only 1 case, mentioned above, was the drug continued postoperatively, but it is thought that in many cases such continuation could and should be carried out. In support of this may be cited the case of a seventy-eight-year-old man in which a combined abdominoperineal resection was done in one stage after routine preparation. Four days postoperatively the end colostomy slipped back into the peritoneal cavity. The bowel was then retrieved and sutured to the abdominal wall. There was undoubted soiling of the peritoneal cavity, but the patient did not develop peritonitis. He was eventually discharged in a satisfactory condition.

low blood concentrations of the drug (measured as sulfathiazole) and in the absence of any toxic manifestations, the simpler routine was thereafter adopted of giving all patients 1 gm. every four hours after the initial dose. In Cases 8 and 14, it will be noted that the blood level was appreciably higher than that in any other case, reaching levels of free drug of 2.040 and 2.681 mg. per 100 cc., respectively. This is due to the fact that these patients were inadvertently given routine doses of sulfadiazine by mouth eighteen to twenty-four hours before these determinations were made.* The figures are interesting in that they show how little phthalylsulfathiazole is absorbed by the blood stream as compared with sulfadiazine.

Results

There were no toxic reactions from phthalylsulfathiazole in this series.

Among the 49 operative cases — fifty-two operations — in which phthalylsulfathiazole was used,

*The routine preoperative use of sulfadiazine as outlined in the section on preoperative preparation was not begun until after the data of the first 19 cases (Table 3) had been collected.

there were 4 cases (8 per cent) with infection. Three patients had wound infection and 1 developed generalized peritonitis and died, a mortality rate of 2 per cent. One of the patients with wound infection received an abdominoperineal resection. The end colostomy slipped back below the peritoneal floor on the fifth postoperative day, but it was almost immediately retrieved, and no peritonitis ensued. A similar accident occurred in another case in which wound infection developed; the mishap was not detected for eight to twelve hours. Colostomy was revised and the patient recovered. These 2 patients had received the drug for four and ten days, respectively, before operation.

The single operative fatality in this group occurred in a patient who had a two-stage operation for carcinoma of the splenic flexure. Following cecostomy, the patient received sulfathiazole for eight days before the second stage of the operation. Extension of the tumor necessitated partial resection of the stomach and splenectomy, as well as resection of the splenic flexure with primary anastomosis. The patient died three weeks postoperatively of peri-

tonitis. The effectiveness of the drug in this case was probably somewhat diminished by the presence of the cecostomy.

SUMMARY

Phthalylsulfathiazole, a new intestinal antiseptic and bacteriostatic agent, after its use in 51 cases was ranked as of definite value as an aid in surgery of the large bowel. Its small dosage, great bacteriostatic activity and low toxicity make it an easy, effective and safe drug to use. Continued use of the drug postoperatively, wherever possible, is advised.

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CHRONIC DISABILITY IN MILD CASES OF TRENCH FOOT

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RELATIVELY little study has been made of the persistent signs and symptoms of trench foot and immersion foot, most papers on this disorder dealing with their acute manifestations.^{1, 2} According to my experience, however, these symptoms may be disabling for at least one year and are apparently not alleviated by any of a variety of therapeutic measures, including psychiatric treatment. At the present time, with relatively large numbers of patients with this condition awaiting disposition at military hospitals in this country, such a study appears timely.

During February and March, 1945, in Italy, an opportunity was presented to study with special attention some of the manifestations of the later stages of trench foot. These cases, all of which were contracted in the Apennine Mountains of Italy during the winter of 1944-1945, were of mild to moderate severity and were on the whole less severe than those encountered during the preceding Italian winter campaign.

Since the later manifestations of trench foot are typified by subjective complaints most difficult to evaluate, an attempt was made to determine what abnormal responses, if any, could be elicited by various stimuli. In the cases studied, within one or two months after onset, the acute manifestations of edema and gangrene or pseudogangrene had disappeared and spontaneous pain, with tenderness of

the soles of the feet, was the chief complaint. The persisting disturbances fell into two main groups — the vascular type, characterized by a tendency to coldness and cyanosis of the feet, and the neural type, marked by pain on firm pressure over the soles of the feet, superficial hypalgesia, loss of proprioception, diminution of temperature discrimination, hyperhidrosis and poor toe-flexion ability.

VASCULAR DISTURBANCES

It is a frequent observation that patients suffering from the later stages of trench foot tend to have cold, sweaty feet that on dependency rapidly develop cyanosis. The following conclusions were reached from studies of this tendency.

When the shoes and socks of patients with trench foot are removed, the feet are found to be devoid of cyanosis, whether the patients have been stationary or moving about and even though the toe-skin temperatures are usually low (20° to 23°C.). On dependency without the constricting shoes and socks, however, cyanosis generally develops within five minutes. It can be made to disappear by elevating the feet, a normal pink color taking its place. Furthermore, on elevation the cyanotic hue can be readily milked out of the toes. If a uniform light-pressure bandage is applied to a toe when it is pink and the foot is placed in a dependent position, the bound toe is seen to be pink immedi-