INTRAPERITONEAL ADMINISTRATION OF SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE

Their Use in the Prophylaxis and Treatment of Peritonitis

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SHORTLY after the introduction of the sulfonamide drugs as antibiotics, they were used intraperitoneally as a prophylaxis against peritonitis. Innumerable reports indicated that they were effective, but most surgeons abandoned their intraperitoneal use when penicillin was made available, because it appeared to be more effective than the sulfonamide compounds. Of these two drugs penicillin appears definitely to be more helpful against colon bacilli, but neither can be classified as being extremely effective against these organisms. Although streptococci and other pyogenic bacteria are occasionally isolated as causative organisms in peritonitis Escherichia coli is much commoner and even when a mixed infection occurs it is usually the predominant organism. Therefore, in the treatment or prophylaxis of peritonitis there would appear to be a need for an antibiotic agent which would be more effective against Esch. coli.

The introduction of the oral use of succinylsulfathiazole in 1941 by Poth and Knotts [1] and, later, phthalylsulfathiazole in 1943 by Poth and Ross [2] led us to investigate the absorbability of these drugs when they were introduced intraperitoneally. Experiments performed by us, as described later, revealed the fact that they were absorbed rapidly from the peritoneal cavity, although they are absorbed only to the slightest extent when given by mouth.

Poth,[3] Poth and Knotts,[4] Streicher [5] and Poth and Ross [6] have shown that when given orally succinylsulfathiazole and phthalylsulfathiazole are capable of reducing the number of bacteria (particularly Esch. coli)

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1. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, Arch. Surg. **44**:208 (Feb.) 1942.

2. Poth, E. J., and Ross, C. A.: Phthalylsulfathiazole, a New Bacteriostatic Agent, Federation Proc. **2**:89, 1943.

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in the feces to a remarkably low number. This has led to a rather widespread oral use of these drugs in colonic surgery. Large doses of the drugs have been administered, without detectable damage to the laboratory animals or to the patients. This has been thought to be merely a reflection of one of the physical properties of the drugs, namely, the low rate of absorption from the gastrointestinal tract. Per gram of drug, phthalylsulfathiazole is about twice as effective as succinylsulfathiazole. Toxic manifestations have been minimal or entirely absent in patients receiving 0.15 to 0.25 Gm. of succinylsulfathiazole or 0.08 to 0.12 Gm. of phthalylsulfathiazole per kilogram of body weight by mouth per day.

EXPERIMENTS ON ANIMALS

Succinylsulfathiazole.—We made a sterile suspension of succinylsulfathiazole in isotonic solution of sodium chloride and, under sterile precautions, injected (with a syringe and needle) 0.25 Gm. of the drug per kilogram of body weight into the peritoneal cavities of 8 dogs. Samples of blood were taken every four hours for thirty-two hours. As shown in the chart (*A*), the maximum level (2.5 mg. per hundred cubic centimeters) was noted at four hours.

None of the dogs evinced signs of toxicity. One dog was explored at the end of twenty-four hours to allow inspection of the peritoneal cavity. There were small clumps of the drug on the folds of mesentery, and this was estimated to represent about 20 per cent of the quantity of the drug placed therein. There was only a moderate amount of peritoneal fluid, and there was no evidence of peritoneal irritation. The incision was closed, and the animal recovered without further difficulty.

The abdomen of a second dog was opened at the end of forty-eight hours and the peritoneal cavity inspected. The succinylsulfathiazole had been completely absorbed, and again there were no signs of irritation. There were a few fibrinous adhesions between the omentum and the site of the needle puncture.

The remaining 6 dogs were operated on at intervals up to twenty-one days and similar observations made. No trace of the drug could be found; likewise, peritoneal irritation was absent or minimal.

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3. Poth, E. J.: The Sulfonamides as Therapeutic Agents in Intestinal Antisepsis: Collective Review, Internat. Abstr. Surg. **78**:373, 1944; in Surg., Gynec. & Obst., May 1944; Succinylsulfathiazole: An Adjuvant in Surgery of the Large Bowel, J. A. M. A. **120**:265 (Sept. 26) 1942.

4. Poth, E. J.; Knotts, F. L.; Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, Arch. Surg. **44**:187 (Feb.) 1942.

5. Streicher, M. H.: Phthalylsulfathiazole, J. A. M. A. **129**:1080 (Dec. 15) 1945.

6. Poth, E. J., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, J. Lab. & Clin. Med. **29**:785 (Aug.) 1944.

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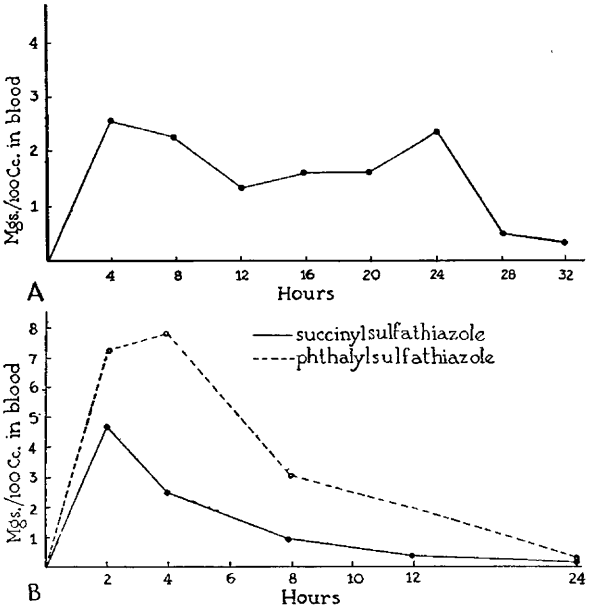
Dog 1 was reoperated on at thirty days, and no evidence of damage to the peritoneal cavity was found. Dog 2 was likewise reoperated on at fourteen days, and similar results were noted.

In order to study the toxic effects of massive doses of succinylsulfathiazole, we injected 5 Gm. of the drug per kilogram of body weight into the peritoneal cavities of 2 dogs. Both were dead in thirty-six hours. Histologic studies revealed diffuse pneumonitis throughout both lungs. There was about 300 cc. of yellow fluid in the peritoneal cavity. No drug crystals were demonstrable in the kidney.



A, blood level of sulfathiazole after intraperitoneal injection of 0.25 Gm. per kilogram of body weight of succinylsulfathiazole in the dog. The graph represents the average of 8 dogs. Note that the blood level is lower but maintained longer than with the smaller dose used in human beings (see *B*). *B*, blood level of sulfathiazole after implantation of 0.1 Gm. per kilogram of body weight of succinylsulfathiazole, as compared with the level following implantation of phthalylsulfathiazole into the peritoneal cavity of human beings at the time of operation. Each graph represents the average in 12 patients.

Into a series of 8 dogs 2.5 Gm. of the drug per kilogram of body weight was injected intraperitoneally. Three of the 8 dogs vomited within one hour after injection, but at no time did they appear acutely ill. One dog died nine days later, and at autopsy it was apparent that the liver and small bowel had been punctured at the time of injection. The dog had struggled violently while the needle was in place, and from the second day on he appeared listless and failed to eat as well as the other dogs under study. There was a walled-off cavity containing about 30 cc. of bile-stained fluid, and there was a localized

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abscess about a loop of ileum. Dissection revealed a small hole in the wall of the bowel. The peritoneum was covered with a fibrinous exudate.

The remaining 7 dogs were killed at intervals up to thirty days. There was no evidence of peritoneal irritation in any of the dogs, and the histologic studies did not reveal parenchymal damage to any of the visceral organs.

Phthalylsulfathiazole.—Into the peritoneal cavities of 4 dogs 5 Gm. of phthalylsulfathiazole per kilogram of body weight was injected as a suspension in isotonic solution of sodium chloride. All 4 dogs vomited within thirty minutes; 2 dogs died within twenty-four hours. Autopsies revealed approximately 300 cc. of yellow peritoneal fluid and diffuse hyperemia of all parenchymatous organs. About 25 per cent of the drug injected was found well distributed throughout the peritoneal cavity.

Six dogs were given 2.5 Gm. of phthalylsulfathiazole intraperitoneally per kilogram of body weight. All 6 dogs vomited within thirty minutes. Two dogs died within twenty-four hours, but the other 4 dogs remained alive and after their initial vomiting seemed to suffer no evil effects.

Four dogs were given 1 Gm. of the drug per kilogram of body weight intraperitoneally. All the dogs vomited but remained alive and well. Two dogs were killed, 1 at seven and another at fourteen days, and histologic sections of the visceral organs were studied. Aside from a mild hyperemia at seven days, no pathologic changes were noted.

INTRAPERITONEAL USE OF THE DRUGS IN HUMAN BEINGS

In a clinical study of the intraperitoneal use of succinylsulfathiazole and phthalylsulfathiazole,[7] a dose was adopted which would be no greater than 0.1 Gm. per kilogram of body weight. Since animals tolerated a dose of at least 1 Gm. per kilogram of body weight, given intraperitoneally, without any evidence of toxic reaction with either drug, the dose of 0.1 Gm. per kilogram of body weight for human beings would appear to be entirely safe.

Up to date we have used succinylsulfathiazole in 28 patients and phthalylsulfathiazole in 23 patients intraperitoneally [8] in a dose of 6 Gm. for an adult, which is approximately 0.1 Gm. per kilogram of body weight. The drug has been dusted in as a powder or suspended in 20 to 30 cc. of isotonic solution of sodium chloride and poured into the peritoneal cavity. Care must be taken lest the drug get into the wound,

7. We are informed by Dr. M. Streicher of Chicago that he has also used both of these drugs intraperitoneally as a prophylaxis against postoperative peritonitis.

8. The drugs were sterilized by heating in a dry oven for four hours at a temperature of 140 C.

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since experiments on animals conducted by one of us (J. Y.) have shown that its presence in a wound will delay healing. This is to be expected since neither of the two drugs, unlike other sulfonamide compounds, is absorbed from subcutaneous tissue.

The patients were watched carefully postoperatively for signs of toxic manifestations, such as hematuria, oliguria, leukopenia, agranulocytosis, nausea, vomiting, headache and mental confusion; specimens of blood were drawn at specified intervals up to twenty-four hours for determinations of blood levels. In none of the patients did we observe any evidence of toxic reaction to either of the two drugs; results of urinary examinations also were consistently normal.

Two cases were of particular interest to us since they gave us an opportunity to study the effect of phthalylsulfathiazole on established peritonitis. One of the patients was a Negro boy, 10 years old, who entered the Research and Educational Hospitals with a history of abdominal pain of five days' duration. Examination revealed general peritonitis arising from a perforated appendix. He had been treated at home with catharsis and enemas, and at the time he entered the hospital he was irrational, dehydrated, toxic and almost preterminal. Since children with perforated appendixes respond so poorly to conservative or delayed surgical treatment, it was thought that operation should be performed as soon as dehydration and electrolyte imbalance could be corrected. After several hours of preoperative treatment, operation was performed; the appendix was removed and an abscess drained although it was obvious that general peritonitis also existed. Culture revealed Esch. coli, hemolytic Staphylococcus aureus and a nonhemolytic streptococcus. Four grams of phthalylsulfathiazole was placed in the peritoneal cavity. The administration of penicillin, which had been started preoperatively in doses of 30,000 units every three hours, was continued. The patient died four days later, and at autopsy the peritoneal exudate was again cultured. The cultures revealed numbers of hemolytic Staph. aureus and nonhemolytic streptococci, but no Esch. coli were found. Another patient illustrated the same point, namely, disappearance of Esch. coli in the peritoneal cavity following implantation of phthalylsulfathiazole into the peritoneal cavity, although streptococci and staphylococci were still present on culture. In a Negro woman, aged 23 years, a spontaneous perforation of the cecum developed at the site of a tuberculous ulcer. At operation, which was delayed twelve hours because of the patient's refusal to give permission for operation, there was generalized peritonitis along with disseminated tuberculous peritonitis. The perforated cecum was exteriorized, and 6 Gm. of phthalylsulfathiazole was implanted in the peritoneal cavity before closure. Culture of material taken at the time of operation revealed Esch. coli, streptococci and staphylococci. Roentgenologic examination of the chest revealed

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minimal tuberculosis of the lungs. At autopsy, three days later, which confirmed the operative findings, culture revealed no Esch. coli but numerous colonies of streptococci and staphylococci. The patient had been given heavy doses of penicillin (300,000 units per day) beginning with the date of operation.

We admit that no conclusions can be drawn from these cases, but since penicillin is known to be much less effective against colon bacilli than against pyogenic organisms one would be inclined to attribute the elimination of the infection with colon bacilli to the phthalylsulfathiazole rather than to penicillin, particularly since we know that it is so effective against that organism in the intestinal tract. However, it is important to note that intensive pencillin therapy failed to eliminate the streptococci and staphylococci in both instances.

ANALYSIS OF RESULTS

In clinical trials on human beings as well as in experiments on dogs, we noted that succinylsulfathiazole and phthalylsulfathiazole were absorbed rapidly from the peritoneal cavity. The peak blood level occurs within the first few hours after implantation.

In none of the patients receiving the drugs in the dose of approximately 0.1 Gm. per kilogram of body weight was there any evidence of toxic reaction. Routine urinary examinations revealed no albumin, red blood cells, crystalluria or any other pathologic change. This freedom from abnormal urinary findings is perhaps explained on the basis that the kidneys do not excrete large amounts of either drug (Poth and Ross [6]) in the free form and that the conjugated form is soluble at a p_H as low as 5.61. Nevertheless, we were careful to insure a daily fluid intake of at least 2,500 cc.

In dogs it had been determined that 2.5 Gm. of succinylsulfathiazole per kilogram of body weight could be used without serious side effects and that 1 Gm. per kilogram of phthalylsulfathiazole could likewise be used intraperitoneally with safety. Hence we felt entirely safe in using 0.1 Gm. per kilogram of body weight in human beings; subsequent observations seemed to justify that dose.

From the previous study by Walter and Cole [9] and others, we know that clumping of the sulfonamide drugs in the peritoneal cavity will lead to a foreign body reaction; accordingly we are careful to distribute the drug diffusely. When the drug is suspended in isotonic solution of sodium chloride, there is less danger of clumping. Neither of the two drugs studied showed any tendency to produce intra-abdominal adhesions, thereby resembling sulfanilamide; it is well known that sulfathiazole and

9. Walter, L., and Cole, W. H.: The Intraperitoneal Administration of Sulfadiazine, Surg., Gynec. & Obst. **76**:524 (May) 1943.

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sulfadiazine produce a few adhesions following implantation in the abdominal cavity, but they disappear after six to ten days.

Determinations of the blood levels of sulfathiazole in patients having 0.1 Gm. succinylsulfathiazole or phthalylsulfathiazole placed in their peritoneal cavities reveal that a peak is reached rapidly (see chart, *B*), but that the peak is maintained for only a short time. This would not appear to be entirely desirable. However, since the purpose of implantation of a sulfonamide drug into the peritoneal cavity is to combat soilage incurred at the time of operation and could not be expected to offer much protection against a leaking suture line, which usually occurs only after a few days, perhaps the need for prolonged exposure is not so urgent. From the standpoint of slow absorption sulfadiazine and sulfathiazole are superior to the two drugs being discussed, but since these two drugs are so ineffective against Esch. coli they have been supplanted by penicillin. Some authors have reported penicillin to be mildly effective against Esch. coli, but our experience with penicillin in Esch. coli infections has been disappointing. Preliminary reports concerning streptomycin are encouraging in infections with colon bacilli; it is therefore possible that this drug given along with penicillin would eliminate indications for intraperitoneal implantation of any drugs.

That phthalylsulfathiazole is effective against colon bacilli in the peritoneal cavity is suggested by histories of 2 cases discussed previously in this report. Penicillin had failed to eliminate the staphylococci and streptococci from the peritoneal exudate in both cases, but the colon bacilli had been eliminated; we are inclined to attribute this effect on the colon bacilli to phthalylsulfathiazole and not to penicillin.

Because of the preliminary nature of this report, we have not attempted to evaluate the efficacy of succinylsulfathiazole or phthalylsulfathiazole in reducing postoperative peritonitis or other complications. In view of the low incidence of postoperative peritonitis in carefully performed intestinal anastomoses, it will be necessary to study several hundred cases before definite conclusions can be reached on this point.

SUMMARY

When succinylsulfathiazole and phthalylsulfathiazole are implanted in the peritoneal cavities of human beings or dogs, they are rapidly absorbed into the blood stream; the average peak level of the two drugs at four hours was 4 versus 5 mg. per hundred cubic centimeters respectively (see chart, *B*). The rate of disappearance from the peritoneal cavity is much more rapid than that of sulfathiazole or sulfadiazine and resembles more closely the rate of disappearance of sulfanilamide. Adhesions of the type which are encountered experimentally for several days after intraperitoneal implantation of sulfadiazine and sulfathiazole (but which later disappear) are not observed after use of either drug.

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Either of the drugs herein discussed can be given intraperitoneally to dogs in a dose of at least 1.0 Gm. per kilogram of body weight, without reaction. We have adopted a dose of 0.1 Gm. per kilogram of body weight for human beings, but, in view of the low toxicity in animals, it would appear that the dose could be increased in human beings over that which we used; we noted no toxic reactions of any type in any of the patients to whom the drug had been given.

Our series of cases is too small to allow us to compare it with a control series, since the incidence of significant postoperative intraperitoneal infection which this therapy would hope to prevent is too small to allow comparison unless several hundred cases were studied. However, since both drugs are known to be extremely effective in reducing the Esch. coli count of the stool when they are given orally, it might be reasonable to suppose that they would also be effective against that same organism occuring as a contaminant following intestinal resection.

We are unable to predict which of the two drugs would be the more effective, but since the blood level following a given dose of each is slightly higher and more prolonged with phthalylsulfathiazole this drug might be expected to be more effective than succinylsulfathiazole.

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