THE USE OF SULFAGUANIDINE AS AN INTESTINAL ANTISEPTIC*

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FROM the studies of Marshall and his co-workers[11] on the experimental and clinical use of sulfaguanidine these facts have been ascertained: (1) Although the solubility of the drug in water is greater than that of other sulfonamide compounds, the drug is absorbed less completely from the gastrointestinal tract. (2) The oral administration of the compound reduces the coliform bacteria count in the feces of human subjects. (3) The action of sulfaguanidine is more specific for coliform organisms within the gastrointestinal tract than is that of other sulfonamide drugs. Thus, with regard to specificity and low absorbability, sulfaguanidine would appear to be a desirable therapeutic agent against the most common bacteria of the large bowel, the coliform organisms. This opinion has been borne out by Firor,[3] Marshall[10] and Lyon.[9]

TABLE I

	Gm. of Compound Added to Feces	Gm. Recovered	Per Cent Recovered
Sulfaguanidine....	3	2.91	97.0
Sulfathiazole.....	3	2.83	94.3
Sulfapyridine.....	3	2.81	93.3

Firor has obtained satisfactory results when the drug was administered therapeutically in the preparation and postoperative care of patients submitted to surgery of the colon. Marshall and Lyon[9,10] likewise reported good results in the treatment of acute bacillary dysentery when the drug was administered early in the course of the disease. Although such reports indicate that sulfaguanidine is a useful therapeutic agent, a more extensive experimental and clinical evaluation of the compound is necessary. This communication presents the experience obtained at the Memorial Hospital in the clinical use of sulfaguanidine.

CLINICAL MATERIAL

For this investigation twenty female* and seven male† hospitalized patients were studied. The average age of the entire group was forty-nine years and ranged from thirty-one to seventy-two. All the female patients except one had recently undergone radical mastectomy for carcinoma of the breast, and she had a chronic radiation ulcer of the chest wall. All males had diseases of the rectum or sigmoid colon. In each of the male patients some type of surgery on the colon was done. Six had carcinoma of the colon or rectum and one had chronic diverticulitis. The patient with chronic diverticulitis and two others of the male group had colostomies as a result of previous surgery. The remaining four patients had carcinoma of the colon. They had not undergone any surgical procedure previous to this study.

METHODS

1. Dosage. In order to evaluate the effect of sulfaguanidine 4 Gm. of the compound were administered orally every eight hours to each patient. This dosage is comparable to that used by Firor[3]—50 mg. per kilogram of body weight.

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II. Laboratory Studies. a. Sulfaguanidine levels in blood and urine were determined by the method of Bratton and Marshall.[1]

The concentration of the free compound in the blood of each patient was determined at least three times weekly. The amount of the acetylated sulfaguanidine in the blood was not measured.

Both acetylated and free forms of the compound were determined in twenty-four-hour collections of urine at least four times weekly in each individual. In addition to the quantitative determination of sulfaguanidine in urine, the urinary sediment was examined microscopically for crystals of the compound.

b. Sulfaguanidine Excretion in Stools. In order to determine the amount of the compound in the feces it was necessary to modify the method of Bratton and Marshall for the determination of sulfaguanidine in urine. This was done in the following manner:

The specimen, collected in a large covered pail, was transferred to a wide-mouthed jar with approximately 1,500 cc. of hot water. Rotary mixing by means of an electric stirrer was carried out for fifteen to thirty minutes until a suspension of uniform consistency was obtained. At the end of this period, the total volume of the fecal suspension was taken and two aliquots of 10 cc. each were measured immediately into graduates for duplicate determinations. Each aliquot was extracted with at least four 50 cc. portions of boiling acetone. The combined acetone extracts were filtered and made to a volume of 250 cc. A 1 cc. aliquot of the yellow filtrate was measured into a test tube containing 0.5 cc. of 8 per cent hydrochloric acid and 8.5 cc. of distilled water. The color was developed as described by Bratton and Marshall.

The following precautions are necessary in order to insure a proper determination: (1) The volume and the aliquots of the fecal suspension must be taken immediately on cessation of stirring; otherwise the suspension will not be uniform. (2) The volume of the fecal suspension must be greater than 1,500 cc. in order that turbidity of the final solution may be avoided.

Calculation:

$$\text{Total Gm. in specimen} = \frac{(S)(CS)}{(U)} \times 0.025 \times \text{volume of fecal suspension.}$$

S represents the reading of the sulfaguanidine standard, U the reading of the unknown, and CS is the concentration of the standard.

c. Hematology. On alternate days determinations of hemoglobin and counts of the erythrocytes, leukocytes and platelets were made.

d. Blood Chemistry. The levels of serum proteins,[22] plasma prothrombin,[23] cholesterol and cholesterol esters,[15] bilirubin and blood urea were determined before, during and after therapy.

e. Bacteriology. A minimum of three stool cultures and colony counts of the coliform bacteria were made of the feces of each patient. These cultures were grown on desoxycholate media. In most patients daily bacteriological studies were made unless for some reason a specimen of feces could not be obtained. An attempt was made in all instances to secure a culture and colony count of coliform organisms in the stool specimen before the drug therapy was started. After administration of the sulfaguanidine was begun no cathartics were given except to those patients who were prepared for surgery of the colon.

A $\frac{1}{10}$ Gm. portion of stool was employed. A $\frac{1}{100}$ dilution of stool previously homogenized with sterile physiological saline was made. Of this dilution 0.1 and 1.0 ml. samples were added to 20 ml. of desoxycholate media and the whole poured into sterile Petri dishes. After forty-eight, seventy-two and ninety-six hours of incubation at 35°C., colony counts on each culture were made.

p-Aminobenzoic acid in concentrations of from 1 to 5 mg. per 100 ml. has been shown to be effective against the bacteriostatic action of sulfapyridine, sulfathiazole

and sulfanilamide.[2,5,8,13,16,19,23] Therefore, 5 mg. of p-aminobenzoic acid were added to 100 ml. of desoxycholate media in order to ascertain whether sulfaguanidine was bacteriocidal or was bacteriostatic for the coliform organisms. Duplicate colony counts were made on the stools using the media containing p-aminobenzoic acid.

RESULTS

The results of this investigation are grouped under the following headings: (1) Studies of the absorption and excretion of the drug; (2) the effect of sulfaguanidine on the coliform bacteria of the bowel; (3) the effect of the compound on the patient; and (4) the use of sulfaguanidine in surgical patients.

TABLE II

Amount of Drug Given	Recovered in Feces		Recovered in Urine	Total Recovery of Dose Given
	First 3 Days	Second 3 Days		
6 Gm.....	2.50 Gm.	0.91 Gm.	0.76 Gm. 0.67 0.30 0.017	
	3.41 Gm. (56.6%)		1.747 Gm. (29.1%)	85.7%
6 Gm.....	3.38 Gm.	0.54 Gm.	0.5 Gm. 0.4	
	3.92 Gm. (65.3%)		0.9 Gm. (15%)	80.3%

1. Absorption and Excretion: a. Recovery of Sulfaguanidine from the Excreta. In order to demonstrate that sulfaguanidine could be determined satisfactorily, two types of recovery experiments were carried out. First, known amounts of sulfanilamide, sulfathiazole or sulfaguanidine were added to feces from normal individuals. Table I demonstrates that recoveries from 93 to 97 per cent were obtained. Secondly, one dose of 6 Gm. of sulfaguanidine was administered to each of two patients. The urine and feces of each patient were collected and analyzed for the drug over a period of six days. Table II presents the results of the excretion of sulfaguanidine in two patients yielding total recoveries of 80 to 85 per cent.

Had the collection of the excreta been carried out for a longer period, it is believed that a somewhat higher quantitative yield might have been obtained. The somewhat lower recovery of sulfaguanidine after the ingestion of the compound is not due to the presence of the acetylated derivative of the drug, since hydrolysis of several extracts of fecal material from different patients gave no increased color reaction. These results indicate that the method employed is satisfactory for clinical studies.

b. Excretion of Sulfaguanidine in Feces. From Table II it is evident that the amount of sulfaguanidine recovered from the stools varies in each patient. This variation appears to be governed, most likely, by the amount of the compound absorbed from the gastrointestinal tract.

Hubbard et al.[7] have studied two patients with biliary fistula to whom sulfaguanidine was administered. In neither patient was there any evidence to show that appreciable concentrations of free sulfaguanidine occurred in bile. No test for the presence of acetyl sulfaguanidine was carried out.* In order to account for the absence of the acetylated derivative in the feces of these patients two possibilities exist: first, that no appreciable quantity of the acetylated derivative of sulfaguanidine is excreted into the gastrointestinal tract through the bile; secondly, that whatever acetylated sulfaguanidine is excreted with the bile is either hydrolyzed by bacterial action or is preferentially absorbed through the walls of the gastrointestinal tract and excreted in the urine.

c. Excretion of Sulfaguanidine in Urine. The free and acetylated sulfaguanidine excreted by each patient in twenty-four-hour periods was determined by the

* The presence of acetyl sulfanilamide has been detected in bile in small amounts.[6]

method of Bratton and Marshall. In 166 determinations the average total sulfaguanidine excretion in the urine was 1.71 Gm. per day. (Fig. 1.) The average daily urinary excretion of acetylated derivative was 0.25 Gm., or 14.6 per cent of the total.

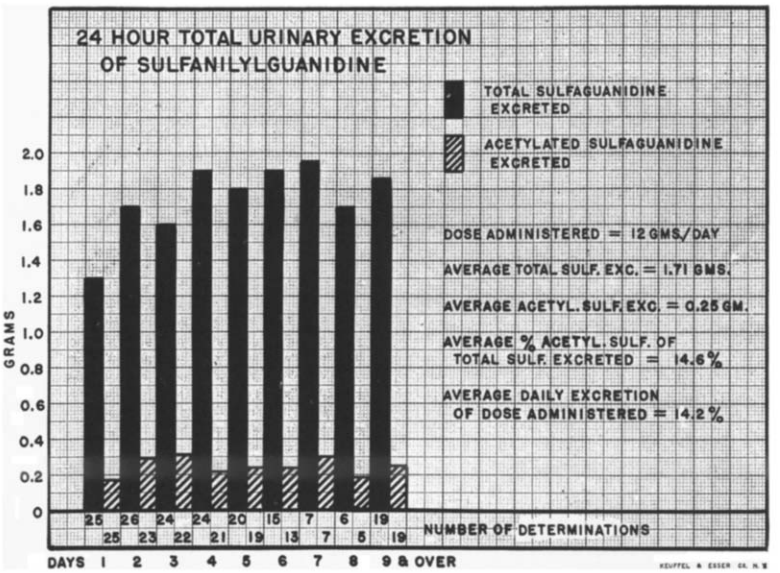

FIG. 1.

The amount of compound recovered from the twenty-four-hour urine specimens of each individual patient varied considerably. The range found for the patients studied was from 0.2 Gm. to 5.6 Gm. Of the sulfaguanidine administered the average excretion in the urine was 14.2 per cent of the total daily dose. Therefore, despite its solubility the greatest proportion of the compound remains in the bowel in a sufficiently high concentration to act as a local chemotherapeutic agent.

d. The Concentration of Sulfaguanidine in the Blood. The amount of absorption of the 4-Gm. doses of sulfaguanidine administered every eight hours is reflected in the blood levels obtained. The levels here reported are only those of free sulfaguanidine. The blood level concentrations ranged from 2 to 4 mg. per cent, and of ninety determinations, the average was 2.1 mg. per cent. In only two instances was a level of more than 5 mg. per cent (5.6 and 5.8 mg. per cent) found, and in neither of these patients were any signs of toxicity noted. The sulfaguanidine concentration in the blood remained low, probably because that portion of the drug absorbed is excreted rapidly in the urine. Abnormal individual absorption or renal dysfunction may result in an accumulation of the compound in the blood but these variables were not observed in any patients of this series.

II. The Effect of Sulfaguanidine upon the Coliform Organisms. A wide variation in the number of coliform organisms on the culture plates is found normally. In the feces of patients used as controls the coliform organisms ranged from tens of thousands to billions of colonies per ml. of wet sediment of stool. This wide variation was noted also in the control coliform colony count from feces of the patients who subsequently received sulfaguanidine. (Fig. 2.)

The addition of p-aminobenzoic acid to the desoxycholate media did not alter the coliform bacteria counts in 99 per cent of all stool cultures made. When no growth of coliform organisms was found on either type of media, incubation was continued for another four days. After this continued period of incubation further growth appeared on the p-aminobenzoic acid media in only two of 168 cultures. It would ap-

pear, therefore, that when the coliform organisms have not grown upon either type of media after four days' incubation under optimum conditions, no further growth can be expected.

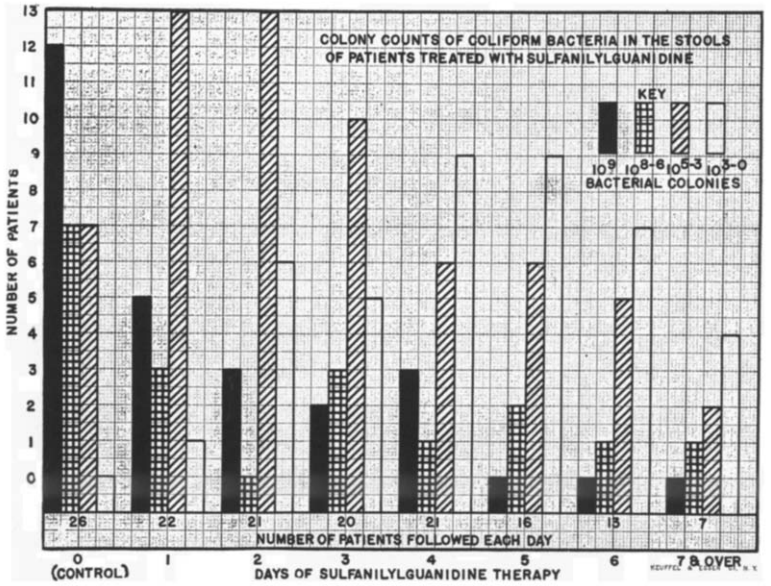

Fig. 2.

When a known sulfonamide inhibitor, p-aminobenzoic acid in concentrations of 1 to 5 mg. per 100 ml., is added to culture media, Janeway[8] has shown that bacteria which are inhibited by the bacteriostatic action of any sulfonamide will grow if any viable organisms are present. From the evidence previously presented, it appears that in those individuals in whom the administration of sulfaguanidine reduced the coliform flora, the action of the compound was bactericidal and not bacteriostatic.

On the whole sulfaguanidine was effective in reducing the number of coliform organisms in the stools. (Fig. 2.) Of twenty-seven patients, eighteen showed a reduction from 10^{9-8} (billions or hundreds of millions) to 10^{3-0} (thousands or no growth) colonies per ml. in the coliform organisms grown from their stools. In the other nine no significant therapeutic effects were obtained.

There was no immediately apparent explanation for the reduction in coliform organisms which was effected in some patients and not in others. The possible explanations are (1) existence of ulcerative lesions within the bowel, (2) the infrequency of administration of sulfaguanidine, and (3) the presence of drug-resistant coliform bacteria in the intestinal flora.

Of the nine patients whose intestinal bacterial flora apparently were unaffected by the administration of sulfaguanidine, four had ulcerative lesions of the sigmoid colon or rectum. The presence of a sulfonamide inhibitor in pus and in other autolysed tissues has been demonstrated.[12] The exudate from an ulcerated bowel lesion may be of such quality, or exist in such quantity, that it will neutralize the bacteriostatic or bactericidal action of sulfaguanidine. It has been shown also that the clinical course of patients with chronic ulcerative colitis is not affected by sulfaguanidine.

After the administration of sulfaguanidine to three patients who had colostomies with intact mucosa above the stoma, satisfactory reduction in coliform bacteria was noted. This result indicates that when the mucosa is intact good therapeutic responses are obtained. Therefore, a marked reduction in coliform organisms can be obtained in the segments of colon above the sigmoid and rectum. This fact may be

important from a prophylactic standpoint. If an ulcerative lesion in the sigmoid is removed surgically, the line of anastomosis thus will not be bathed with intestinal contents which contain excess coliform organisms. Such organisms are inhibited likewise in the postoperative period when sulfaguanidine is administered.

No explanation is at hand for the failure of sulfaguanidine to reduce the coliform bacteria count in the stools in the remaining five of nine patients. It was not determined whether or not the intestinal bacteria of those five were abnormally resistant to the drug.

From the accumulated data* it is evident that no constant reduction in the total number of coliform organisms were obtained. Neither was there any uniformity in the rate of reduction of the bacteria. In several patients it was found that after therapy had been administered for several days the number of coliform organisms was decreasing rapidly. Then, for some unknown reason, the colony count would increase temporarily to about pre-therapy levels, but eventually would decrease again and remain at low levels. In some instances no coliform organisms could be cultured from the last stool specimen examined.

In summary, a noticeable effect of sulfaguanidine upon the coliform organisms usually was apparent from three to four days after therapy was instituted. The colony counts remained low after that time except for the occasional culture in which there appears to be an "escape" from the bactericidal action of the drug. The maximum effect of continued sulfaguanidine therapy is obtained within five to six days. When therapy was discontinued a steady rise in the coliform bacteria count began and reached pre-therapy numbers in two to three days.

It would appear, therefore, that the optimal time for surgery of the colon in patients who receive sulfaguanidine as a prophylactic agent would be from five to seven days after the use of the compound was started. Theoretically, the postoperative sulfaguanidine therapy should be started from twelve to twenty-four hours after surgery.

III. The Effect of Sulfaguanidine on the Patient. a. Effect on the Blood. Complete blood and platelet counts were done on alternate days in the patients studied. Neutropenia, agranulocytosis or hemolysis never were noted. In only one patient was a significant change found in the hemogram after the administration of sulfaguanidine.

In that one patient a reduction of the hemoglobin from 65 to 49 per cent (normal 13.8 G) was associated with a fall in the erythrocytes from 3.5 to 2.9 millions. There was no significant reduction in the leukocytes. This anemia developed after administration of 48 Gm. of the compound given over a period of four days. The blood level of sulfaguanidine was never above 0.5 mg. per cent and no rise in bilirubin was noted. There was no evidence of hepatic dysfunction as determined by an increased ratio of cholesterol to cholesterol esters, or by a fall in the concentrations of serum proteins or plasma prothrombin. Subsequently, a study of the bone marrow revealed it to be moderately hypoplastic. Unfortunately, a bone marrow examination had not been made before sulfaguanidine therapy.

Since the amount of the compound absorbed by this patient was only 1.7 Gm. and represented only 3.4 per cent of the total dose administered, it was probable that the patient was sensitive to the drug. The anemia persisted for four weeks despite the parenteral administration of 45 units of concentrated liver extract per week and ingestion of 45 gr. of ferrous sulfate per day.

b. Effect on the Liver. In order to detect the possibility of hepatic damage after use of sulfaguanidine the following studies were made:

In twenty-two of the patients serum protein values were determined both before and after sulfaguanidine therapy. Five

* Due to lack of space a large table presenting all the data outlined in the text of this article has not been included.

patients had pre-therapy levels below the normal value of 6.5 Gm. per 100 ml. Significant decreases in the serum protein values below the initial values were not found in any patient.

In eighteen patients the ratio of free to total cholesterol in the serum was likewise determined before and after therapy. A normal ratio of from 25 to 33 per cent was noted in every patient.

In sixteen patients no retention of bilirubin was observed.

In twenty six patients the plasma prothrombin was determined. A decrease of prothrombin values of 20 per cent was considered to be significant. Five of the twenty-six patients developed significantly low levels during the course of sulfaguanidine therapy.

It was important, therefore, to determine whether the development of hypoprothrombinemia was due to hepatic damage[17,18,21] or to some other cause. It has been accepted that vitamin K is synthesized from dietary factors by the activity of bacteria in the intestine,[4,14] and it was possible that the administration of sulfaguanidine destroyed those organisms in the intestine which are responsible for the synthesis of vitamin K. To ascertain the facts concerning this question two of the five patients with hypoprothrombinemia were given 2 mg. of synthetic vitamin K_1 (2-methyl-1, 4-naphthoquinone) parenterally. The administration of this compound was followed in both by a rapid return of the plasma prothrombin values to the pre-therapy levels. The three other patients were not given vitamin K, but when the sulfaguanidine was discontinued a rise in the plasma prothrombin levels followed within four days. This experiment would indicate that the hypoprothrombinemia which followed sulfaguanidine administration was not due to a deranged fabrication of prothrombin by the liver, but to a decreased synthesis of the vitamin K by the intestinal flora. This conclusion is supported by the finding that in every patient who showed a decrease in plasma prothrombin a significant reduction in the coliform bacteria count of the stools was found.

The values of serum proteins, the ratio of free to total cholesterol, and the values of bilirubin and plasma prothrombin, determined in a significant number of patients, indicated that no significant alterations in liver physiology could be attributed to the use of sulfaguanidine.

c. Renal Function. Despite the fact that a relatively small percentage (14.2 per cent) of the total amount of sulfaguanidine administered was excreted in the urine, signs of renal irritation were encountered in three patients. Each of these three showed microscopic hematuria which disappeared in three days after the fluid intake was increased. In the urine of one patient casts of sulfaguanidine crystals were found, and this cylindruria was associated with tenderness over the left kidney.

At some time during therapy every patient had sulfaguanidine crystals in the urine, but the number of crystals present varied considerably.

The blood urea concentration was determined in twenty of the twenty-seven patients. No patient developed concentrations of blood urea above those initially found.

d Other Toxic Manifestations. Of the other signs or symptoms which might be attributed to the use of sulfaguanidine, only nausea, vomiting and vertigo were encountered. Nausea and vomiting were observed in two patients, but were not severe enough to make it necessary to discontinue therapy. Two patients complained of vertigo, but no other findings were present to suggest irritation of the central or peripheral nervous systems. Cyanosis, skin eruptions, or the development of fever or jaundice never were seen.

IV. Use of Sulfaguanidine in Surgical Patients. In seven patients surgery of the colon was done. Briefly, the case histories of these patients are as follows:

Case I. This patient had a large ulcerated carcinoma of the rectum. After six days of sulfaguanidine therapy the effect upon the

coliform organisms was equivocal. There was evidence of renal irritation. Many red blood cells were found in the urine together with a large number of crystals of sulfaguanidine. The tumor was inoperable. A colostomy was made. The patient made an uneventful convalescence.

Case II. This patient had an extensive ulcerated carcinoma of the rectum. With three days of therapy no effect on the coliform organisms was noted. The tumor could not be resected. A colostomy was made. There were no postoperative complications.

Case III. This patient had a one-stage abdominoperineal resection for a large ulcerated carcinoma of the rectum. No effect on the coliform organisms was noted after four days of sulfaguanidine therapy. Renal irritation was indicated by the presence of many red blood cells and crystals of sulfaguanidine in the urine. The contents of the resected loop of bowel was cultured and a colony count for coliform organisms showed 100,000 colonies. The convalescence was uneventful.

Case IV. This patient had a resection of the sigmoid for carcinoma with establishment of bowel continuity by a primary aseptic type of anastomosis. After three days of preoperative sulfaguanidine therapy there followed a reduction of the bacterial content of the stool from a count of billions to one where no coliform organisms were found by culture in the stool specimen taken just previous to surgery. Sulfaguanidine was not administered postoperatively. The patient had an uneventful convalescence and was discharged on the sixteenth postoperative day. The bowel content of the resected loop was cultured and contained four million colonies of coliform bacteria per ml. of wet sediment. This patient illustrates the difficulty which is encountered in the evaluation of the effect of sulfaguanidine. It is quite possible that this patient would have done well without sulfaguanidine therapy.

Case V. This was a seventy-two-year-old male who had two previously unsuccessful attempts at closure of a colostomy which followed a Mikulicz type of resection for carcinoma of the transverse colon. A large ventral hernia with a marked protrusion of the bowel had developed around the midline colostomy.

After six days of sulfaguanidine therapy the stool culture contained only 1,000 colonies of coliform organisms. The peritoneal cavity was opened. A side-to-side *open* anastomosis of the loops of colon leading to the colostomy was made, and the large colostomy stoma was closed. The entire colon was replaced in the peritoneal cavity. Seven Gm. of sulfanilamide were placed along the lines of anastomosis. Sulfaguanidine was started twenty-eight hours postoperatively. The postoperative temperature was 101°C. on the first postoperative day, and thereafter never over 100°C. No signs of peritoneal irritation developed and the wound healed per primam. In this instance the drug probably did contribute to the smooth convalescence.

Case VI. This patient was given sulfaguanidine for sixteen days before closure of a colostomy. This colostomy had been constructed as a result of a Mikulicz resection of the sigmoid for chronic diverticulitis and bowel obstruction. A marked reduction in coliform bacteria had been effected by sulfaguanidine therapy. The operative wound healed per primam without any signs of inflammatory reaction about the wound. On the eleventh postoperative day a small fistula developed but readily closed without further operative interference. This patient had not received the drug during the postoperative period.

Case VII. After seven days of drug therapy the stool count for this patient was reduced from millions of colonies to 3,000 colonies on the day preceding surgery. The colostomy was closed and sulfaguanidine was continued postoperatively. The first stool specimen, passed five days after surgery, showed the absence of coliform organisms. The prothrombin value decreased to 50 per cent. Two mg. of 2-methyl-1,4-naphthoquinone were given parenterally and the prothrombin increased to 81 per cent.* The wound healed per primam without any trace of inflammatory reaction. The temperature was never over 100°C. at any time during convalescence.

The effect sulfaguanidine had upon the clinical course of these patients is difficult to evaluate. Any or all of the patients may have done well regardless of the prophylactic use of the drug.

DISCUSSION

The problem of the adoption or rejection of a new member of the sulfonamide

* This patient is not considered in the group of patients discussed previously, as surgery may have been a contributing factor in lowering the prothrombin value.

group must be approached by determining whether or not the compound really is useful therapeutically in a group of conditions for which it was proposed. It is also necessary to discover the fate of the compound, its actual mode of action, and whether or not its therapeutic administration is attended by the production of any toxic effects on the patient.

From the studies presented of absorption and excretion of the compound, it is evident that there is a marked variation in the amount of compound absorbed in each individual patient. However, unlike other sulfonamide compounds in general use, sulfaguanidine is relatively poorly absorbed from the gastrointestinal tract. Thus it remains in the bowel in a sufficiently high concentration to act as a local chemotherapeutic agent. That portion of the compound absorbed is rapidly eliminated in the urine and high blood concentrations are not usually found.

Sulfaguanidine therapy did produce a marked effect upon the coliform intestinal flora in a significant number of patients. Alteration of the intestinal flora in some patients appears to retard the synthesis of vitamin K in the bowel and hypoprothrombinemia results. Reduction of coliform bacteria by sulfaguanidine in the adult results in a condition analogous to that found in hemorrhagic disease of the newborn. The prompt establishment of a bacterial flora in the newborn causes a rise in the prothrombin, probably as a result of the production of vitamin K.[14] Likewise the withdrawal of sulfaguanidine is followed by an increased number of coliform organisms and a rapid rise of the plasma prothrombin to normal values.

Although no patient developed a hemorrhagic crisis, a tendency to such a complication might well have been present. It is, therefore, important that the plasma prothrombin level be checked routinely before patients are subjected to bowel surgery when sulfaguanidine has been administered preoperatively.

In this study sulfaguanidine did not cause any abnormalities in the hepatic functions measured, namely, the maintenance of a normal ratio between the free and esterified cholesterol, excretion of bilirubin, and the synthesis of serum protein and plasma prothrombin.

Sulfaguanidine may be toxic to the hematopoietic system of some patients. This finding was observed in but one instance in this study.

Although signs of renal irritation were observed in three patients, it appears fortuitous that no serious renal complications were encountered, as crystalluria was present in every patient. Oliguria, retention of nitrogenous products or signs of renal colic were never observed.

When the volume of urine excreted is low, crystalluria might present a serious hazard. The low solubility of the acetylated sulfaguanidine might lead to precipitation of crystalline deposits along the urinary tract. The maintenance of a sufficiently high fluid intake, therefore, is imperative in order to prevent massive crystalline concretions.

Other toxic manifestations in this study were relatively unimportant. The rapid elimination of the absorbed portion of the compound through the urinary tract may explain the infrequency of general toxic manifestations.

The experience obtained here of the practical application of sulfaguanidine to bowel surgery is limited. The compound appears to be of some value in selected cases. This conclusion is in agreement with the experience of Firor. Prophylactic use of sulfaguanidine thus far has its greatest merit when administered to patients who are prepared for surgery of the colon. The drug is much more effective when there are no ulcerative lesions of the bowel. Sulfaguanidine may be expected to be of use in uretero-intestinal anastomosis, closure of colostomy stomas, and in restoration of bowel continuity in the two-stage types of colonic resections when the bowel may have to be replaced in the peritoneal cavity.

In most patients a reduction in the number of coliform bacteria in the stools can be expected. In those patients whose coliform flora are not diminished markedly, the toxicity of sulfaguanidine is not sufficient to preclude its trial.

Further work on a large number of patients is needed to establish that rôle the prophylactic use of sulfaguanidine might play in the reduction of morbidity and mortality in elective surgery of the colon. The fact is to be emphasized that a rigid control study of the effect of sulfaguanidine on the bacterial flora of the bowel must be made in every instance.

SUMMARY AND CONCLUSIONS

1. A method for determination of sulfonamide compounds in the feces is presented. A mean average of 14.2 per cent of the total administered compound is eliminated in the urine. Usually the blood level concentrations remain low, probably because the drug is rapidly excreted in the urine.

2. The administration of sulfaguanidine markedly reduced the coliform organisms in the bowel in eighteen of twenty-seven patients.

3. When ulcerative lesions of the bowel are present, a significant reduction in the coliform organisms is not obtained. This fact would limit the beneficial results which could be expected from the use of the drug.

4. The use of sulfaguanidine resulted in an alteration of the blood picture in only one of twenty-seven patients. Nevertheless, it is advisable to check the blood counts of those who receive the compound in order to detect the occasional patient whose hematopoietic system is sensitive to sulfaguanidine.

5. The administration of this compound caused no other significant toxic reactions in twenty-six of twenty-seven patients.

6. Sulfaguanidine by its action of depressing the coliform bacteria interferes with the synthesis or absorption of vitamin K in some patients.

7. Crystalluria with subsequent formation of concretions might be considered a hazard but this complication can be overcome by giving adequate fluids.

8. Sulfaguanidine is not the ideal chemotherapeutic agent for intestinal antisepsis. A sulfonamide which can destroy all the intestinal bacteria and yet have the slow absorption and low toxicity of sulfaguanidine is to be desired.

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CERVICAL block, deep or superficial, should be completed about twenty minutes before the incision is to be made so that the nerve trunks can become sufficiently affected. Sometimes relaxation of the cervical muscles is so marked after the cervical nerves have been blocked that the patient cannot move his head without moving his shoulders.