THE USE OF SULFANILAMIDE IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS

Preliminary Report of 11 Cases

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In the consideration of a new form of therapy for chronic ulcerative colitis it is well known that one year's experience and its use in eleven cases does not justify a final appraisal. The natural remissions of symptoms characteristic of this disease have been responsible for inaccurate appraisal of treatment in the past, unless evaluated in terms of repeated examinations over years of time and by independent investigators. On the other hand, this is an unusually serious disease and when the initial response to a new form of treatment is unusually favorable, we believe others should have the advantage of this experience before awaiting final appraisal.

In our experience, cultures made from rectal scrapings and stools have so commonly shown the presence of various strains of streptococci that a therapeutic trial with sulfanilamide seemed logical.

In eight of our eleven cases we found the initial response to sulfanilamide therapy more satisfactory in a shorter period of time than has been our experience with other forms of medical treatment. Since the progress proctoscopic examinations have revealed unexpected improvement if not normal findings, without scar formation, we believe this group of patients must have had unusually superficial involvement of the wall of the rectum and colon. Heretofore, although the patient had had a complete remission of symptoms, if a proctoscopic examination were done during the remission, the findings were unfortunately too often the same as those visualized at the time of the acute exacerbation of the disease.

The "regional" or so-called "right-sided" form of chronic ulcerative colitis has been encountered in 7 per cent of our cases. Operative procedures early in the course of the disease are the therapeutic methods of choice in these instances. The present communication deals with the remaining 93 per cent, the so-called "universal type," wherein the disease starts as a diffuse inflammation of the rectal mucosa and extends upward in the colon. When treating this form we now believe a two or three months' therapeutic trial with sulfanilamide, as well as other forms of medical management, closely checked by progress proctoscopic examinations (regardless of relief or continuance of symptoms), is indicated before considering surgical procedures, unless contraindications to the use of the drug or obvious complications which demand

surgical intervention exist. The extensive work done by Bargen[1] has resulted in immeasurable clarification of many aspects of this disease, including the definite indications for surgical intervention.

The incidence of chronic ulcerative colitis is increasing, probably due to the more frequent use of stool, proctoscopic, and roentgen examinations of the colon. Universal acceptance of a single etiologic agent has not been established. Sulfanilamide has been employed with excellent results in the treatment of so many types of infectious processes that its use in the treatment of this disease was only a matter of course.

In reporting the results secured from any form of management of this disease, we believe certain criteria and classifications should be used, such as those suggested by Kiefer[2], namely, Group 1, the nontoxic, nonsclerotic group of cases; Group 2, the nontoxic, sclerotic group; and Group 3, the toxic group wherein fever, nausea, vomiting, rapid pulse and prostration, as well as leukocytosis, are present. The mortality rate and the surgical indications are, of course, greatest in the third group. The chief characteristic of the disease is its variable severity. Kiefer has emphasized the fact that its variable severity is probably most important in determining the final outcome of an individual case, and is probably more important than the apparent extent of the disease as determined by roentgen examination. When treating patients belonging to the first two groups, more time may reasonably be allowed for medical management before considering the use of surgical procedures than is the case when dealing with patients belonging to the third group.

Case Reports

Case 1: (Nontoxic, nonsclerotic). A man, 27 years of age, entered the clinic complaining of recurring attacks of lower abdominal cramps, tenesmus, and four to ten loose stools daily, occasionally containing blood. These symptoms had been present for ten years. Each attack varied in duration from several days to several weeks, and recurred at least twice a year with complete remission of symptoms between attacks. There was no history of chills and fever and there was no loss in weight.

The findings on stool and proctoscopic examinations were characteristic of chronic ulcerative colitis; in fact, Dr. Thomas E. Jones reported the proctoscopic findings as showing the late stage of the disease. The roentgen examination of the colon revealed normal findings except spasticity of the left colon. Sulfanilamide, 45 grains daily, was given by mouth, and since repeated studies of the blood did not show any findings which would contraindicate the use of the drug, it was continued for two months. Proctoscopic examination at this time was reported as showing "practically a normal rectal mucosa; bleeds only on very rough swabbing." There was complete remission of symptoms which started on the tenth day of treatment and has continued to and at the end of one year. After the sulfanilamide was discontinued, small retention enemas of colloidal aluminum hydroxide and kaolin[3] were used three times weekly for two

months. The proctoscopic findings were then entirely normal and have remained so up to the time of this report, one year after starting sulfanilamide therapy.

Although there was a history of symptoms for ten years, there was apparently a relatively low degree of severity of the process. The patient remained ambulatory and the disease did not interfere with his occupation.

Case 2: (Nontoxic, nonsclerotic). A man, age 39, had symptoms and objective findings similar to those mentioned in Case 1, except that, five years prior to entrance, the symptoms had been present for two months, followed by a remission which lasted until four weeks preceding our examination in March, 1936. During these four weeks the patient stated that he had "innumerable stools" containing blood, as often as every 20 minutes during the daytime and every half hour during the night hours. He "lived in the bathroom." There was no history of chills and fever, and he had lost only five pounds in weight. He was unable to work and an anti-amebic therapeutic test, extending over several weeks, resulted in no improvement. On April 6, 1936, the subcutaneous use of an autogenous vaccine was started. On May 16, 1936, after having had daily administrations of the vaccine, the symptoms were somewhat relieved and the patient was not seen again until October 25, 1937. At this time he stated that he had been well until two weeks prior to re-entrance, but during the two weeks "all of the former trouble has recurred." Proctoscopic examination revealed extensive, acute involvement of the rectal and lower sigmoid mucosa, and roentgen examination showed extension of the disease to the mid-descending colon. Sulfanilamide (in the dosage mentioned in Case 1) was started October 27, 1937, at which time the patient was having at least 20 stools in 24 hours, many of which contained blood. Twelve days later he was having not more than four stools in 24 hours and felt "excellent"; four days later he was having only one stool in 24 hours and he returned to work. After he had had 45 grains of sulfanilamide daily for 44 days the proctoscopic findings were practically normal. There were no ulcers and no bleeding on rough swabbing. On December 24, 1937, when the sulfanilamide was stopped, he was having no abdominal distress, was on a full diet, and was having not more than two formed stools daily. This, as well as normal proctoscopic findings, have continued to approximately the date of this publication.

This case is quoted to show the difference in the time element of response to treatment to sulfanilamide therapy as compared with that of autogenous vaccine, all other factors remaining approximately the same.

Case 3: (Mildly toxic). A housewife, 42 years of age, had had recurring attacks of diarrhea, "20 or more stools, often containing blood, in 24 hours," during the preceding six years. Fever had been present and the patient was bedridden during several of the attacks. One attack had lasted six months and another 16 months. Proctoscopic examinations during these times were always reported as showing "typical chronic ulcerative colitis." Two years prior to entrance she had a skin eruption and a diagnosis of dermatitis herpetiformis was made. Allergic investigation was instituted and the eliminaton of allergens as determined by skin tests resulted not only in the relief of the skin trouble but also some improvement in the symptoms due to the colitis. Extensive treatment with autogenous vaccines apparently had had no permanently beneficial effect.

Proctoscopic examination at the time of admittance revealed an extensive process involving the entire rectal mucosa. Roentgen examination of the colon did not show evidence of abnormality above the sigmoid colon. During the following three months the patient used aluminum hydroxide and kaolin retention enemas daily during the first month and approximately three times weekly thereafter with complete relief of symptoms, but the proctoscopic findings at the end of this time were practically the same as observed at the time of admittance.

The use of sulfanilamide was started in December, 1937, and the dose, by mouth, did not exceed 45 grains daily. The patient remained ambulatory throughout the course of treatment. Twenty-four days later, chills and a fever ranging between 102 and 104° F. developed. These were attributable to nothing other than the use of the drug and three days after its discontinuance the temperature returned to normal. Since that time the patient has had only one or two formed stools daily and has not observed blood or pus. Much to our surprise, proctoscopic examination on February 9, 1938, revealed considerable improvement, and a recheck examination on March 25, three months after sulfanilamide was used, revealed normal findings except for a small granular area about one inch proximal to the anus.

Since this patient gave a history of fever and severe prostration during several of the exacerbations of symptoms, her case has been included in the Group 3 or toxic group. Although many forms of treatment had been used during six years, including management from the standpoint of allergy as determined by skin tests, the use of autogenous vaccines and the use of aluminum hydroxide and kaolin retention enemas (three months), to our knowledge, proctoscopic findings had never shown improvement until sulfanilamide was used.

Case 4: (Severely toxic.) A housewife, 51 years of age, was admitted directly to the hospital in an acute fulminating attack of ulcerative colitis. During the preceding 10 days she had had countless stools night and day with continual tenesmus. The temperature varied between 100 and 102° F. during the first week in the hospital. The stools contained much pus, blood, and mucus. The proctoscopic examination revealed the presence of an acute ulcerative colitis as far as the scope could be passed. The roentgen examination, using the barium enema, revealed evidence of typical infiltration characteristic of a diffuse ulcerative colitis from the rectum to the hepatic flexure of the colon. She had lost 30 pounds in weight during the previous three months, due in part to a marked anorexia and vomiting at irregular intervals, as much as four times daily. The exact duration of the disease could not be determined. Although the diarrhea had been of relatively short duration she had not been well for eight months because of malaise and anorexia.

The patient was in the hospital approximately one month and during this time received five blood transfusions, parenteral liver extract, and vitamin B_1. Due to the lack of free hydrochloric acid in aspirated test meals, 1 drachm of dilute hydrochloric acid was given constantly with each meal as soon as she was able to tolerate food by mouth.

Sulfanilamide and soda bicarbonate, of each 40 grains daily, were given for 20 days. Within two weeks from the time these medications were started, the temperature became normal, appetite and gain in weight were restored, no more than two stools in 24 hours were passed, and these factors remained the same

during the remainder of the hospital sojourn. Aluminum hydroxide and kaolin retention enemas were used during the final two weeks, at the end of which time there was marked improvement in the proctoscopic findings.

Four months later she reported that her general condition had remained excellent. She had been entirely free from symptoms since leaving the hospital and had gained 23 pounds in weight. The aluminum hydroxide and kaolin retention enemas had been used twice weekly for two months but during the two months prior to re-entrance she had not used these or any other type of medication. The stools, proctoscopic, and blood findings were entirely normal.

This case report is given as an example of an acute fulminating toxic type of ulcerative colitis, the type which may prove fatal. The response to therapy to date has been unusually gratifying.

Another group of four cases responded similarly to the use of sulfanilamide therapy. Two of these are classified as belonging to the nontoxic, nonsclerotic group and did not present evidence of extension of the disease above the lower sigmoid colon. The other two cases are included in the severely toxic group and there was roentgen evidence of involvement of the entire colon in both instances. Additional details pertaining to each of these four cases are not presented because of the similarity to those quoted, according to the classified grouping in each instance, in the first four case reports.

There was no response to sulfanilamide therapy in three cases. These belonged to the severely toxic group and there was extensive involvement of the colon in each instance. Other forms of medical management have proved effective to date, so that no surgical procedure has been used in the eleven cases selected for this investigation.

Summary of Results

Sulfanilamide therapy was used in the treatment of chronic ulcerative colitis in eleven cases. An unusually rapid and satisfactory initial response, which has been maintained to the date of publication, was obtained in eight of the eleven cases. In those in whom the use of the drug proved effective, the results were unusual because we have not seen a similar response while using other forms of medical therapy in similar conditions. Of the eight cases wherein a favorable response was obtained, four were ambulatory patients, belonging to the nontoxic, nonsclerotic group in whom there was no evidence of extension of the disease above the sigmoid colon except in one instance where there was involvement up to the mid-descending colon. The other four were toxic cases, one was mildly toxic and did not have evidence of involvement above the sigmoid colon, while three were severely toxic and were admitted directly to the hospital in the acute fulminating stage of the disease, with involvement of the colon up to the hepatic flexure in one case and involvement of the entire colon in two cases.

Sulfanilamide therapy was not effective in three severely toxic cases, in each of which there was extensive involvement of the colon.

Comment

Final appraisal of the use of this drug must, of course, await the "follow-up" repeated stool, proctoscopic, and roentgen examinations of the rectum and colon, extending over years of time, as well as the continued relief of symptoms. At the time of the initial examination, we believe the physician should spend more time than is customary in acquainting the patient with the characteristics of the disease. The patient must understand that a remission of symptoms does not signify a "cure," and that the only criterion of value, so far as the likelihood of his not having additional acute exacerbations of the disease is concerned, can be established only by making the progress examinations mentioned.

At the time of the initial examination, regardless of whether there is evidence of amebiasis on stool and proctoscopic examinations, we commonly place the patient on a therapeutic test, using anti-amebic therapy. Only in this way do we conclude that the Endameba histolytica is not the etiologic agent.

Our next step in therapy, at the present time, is a therapeutic trial with sulfanilamide. If the drug is well tolerated we believe its use should be continued for two or more months in relatively low dosage before deciding that it is ineffective. Recently, we have given sulfanilamide by rectum on alternate weeks in certain individuals, with satisfactory initial results.

In the ambulatory patients belonging to the nontoxic, nonsclerotic group of cases, we have made progress proctoscopic examinations while the patients were receiving only sulfanilamide therapy and an intestinal low-residue, high-vitamin diet. The patients in this group were able to resume their usual occupations after receiving sulfanilamide for 16 days or less.

In the severely toxic group in which the patients were admitted directly to the hospital in the acute fulminating stage of the disease, repeated blood transfusions, parenteral administration of vitamins, and other measures heretofore commonly used in this group of cases, aside from the use of sera and vaccines, were utilized. These features were considered on a comparative basis in the appraisal of the initial response to sulfanilamide therapy.

Clinicians who are particularly interested in treating this serious and disabling disease know that any therapeutic procedure which has shown promise of relieving the patient's disability must be given

adequate trial. Too often no change is noted in progress examinations, regardless of the complete remission of symptoms. Therefore, the clinician commonly uses several types of treatment concomitantly or in sequence, and in the end has difficulty in the final appraisal of any one procedure. This applies particularly to the severely toxic cases in which the mortality rate is the highest. Since the use of sulfanilamide is a new procedure, we have discontinued this form of therapy as soon as we considered it had been given an adequate trial. In many instances in both groups quoted, aluminum hydroxide and kaolin retention enemas have been used during the *convalescent* stage after a favorable response to sulfanilamide therapy has been shown by proctoscopic examination as well as a remission of symptoms. The preparation used at first was that described by Eyerly and Breuhaus[3], but due to the occasional occurrence of hard stools this was discontinued in favor of a similar preparation to which mineral oil had been added, as advocated by Fradkin[4]. At present we are using two ounces of this preparation* diluted with two ounces of distilled water or larger quantities, depending upon the extent of the disease, every one to three days during the convalescent stage of the disease as determined by progress proctoscopic examinations. The use of this preparation during the acute phase has not proved as effective as sulfanilamide in our experience.

Disadvantages to the Use of Sulfanilamide

The possible toxic effects resulting from the use of sulfanilamide have been emphasized in many papers published in the Journal of the American Medical Association during the past year. In two of our patients a high fever developed between the tenth and twenty-fourth day of its administration. In these instances, no deleterious effect has been observed since its immediate discontinuance. A common observation has been that patients belonging to the severely toxic group have pallor or cyanosis during its administration, but this has not been found to be a contraindication to its use. However, the patient's relatives and friends should be warned of this possibility before the drug is started. In every instance, repeated studies of the blood have been made and the most common finding has been a lowering of the hemoglobin content of the red blood cells. Blood transfusions in the toxic cases and adequate administration of iron products in the nontoxic cases, during the intervals when sulfanilamide was not used, have counteracted this tendency in our more recent experience. Since sulfanilamide is eliminated in the urinary tract, we now believe tests of renal function, including the urea clearance test, should be done before considering

* Now available on the market as Kaomagma, Rectal, John Wyeth & Brother, Inc., Philadelphia.

this mode of therapy. The value of a high fluid intake to aid in kidney excretion has been demonstrated in cases showing evidence of toxicity to the drug. In certain instances, the toxic effects varied according to the method used in the administration of the drug.

Mode of Administration

At first sulfanilamide was given orally in nontoxic cases and parenterally in severely toxic cases at the start of the treatment. An attempt was made to maintain a blood level between 8 and 10 mg. per 100 cc. of blood. Toxic effects were quite commonly observed and we learned to use this drug with caution. General malaise, headache, anorexia, nausea, and increased diarrhea occurred and patients were forewarned of this possibility. On the other hand, we believed that unless a relatively high concentration in the blood was maintained the drug was not being given an adequate therapeutic trial. Skin manifestations were not uncommon. We were searching for an adequate blood sulfanilamide level which could be maintained over a relatively long period of time, longer than had been the custom with its use for other types of infections.

More recently we have found that the administration of the drug by retention enema has not been so commonly associated with the toxic effects mentioned, that adequate absorption occurs as determined by blood sulfanilamide determinations, and that although the blood level is lower than mentioned above, equally effective results have been obtained as shown by progress proctoscopic examinations, aside from the relief of symptoms. In the severely toxic cases and in patients having many loose stools per day, opium suppositories have been used before the rectal administration and small quantities were given at a time at the start of treatment. With clinical improvement, larger quantities were retained until one or two retention enemas fulfilled the usual routine 24 hour dosage of not more than a total of 45 grains (powder form) in one pint of distilled water, warmed to body temperature. In our experience to date this dosage has resulted in maintaining a blood sulfanilamide level of 5 to 7 mg. per 100 cc. of blood in most instances, but the degree of absorption of course depends on the severity and extent of the diseased process.

Because of the tendency to the production of a hypochromic anemia while using sulfanilamide, which we have observed when the drug has been used over several months of time and no other toxic effects were demonstrable, we now commonly give the drug by retention enema intermittently, with high iron therapy in the intervals. The incompatibilities of sulfanilamide with other drugs, particularly the sulphates, is now well recognized.

Sulfanilamide is not a harmless drug to be dispensed without supervision by a physician. Obvious surgical indications must be excluded before this form of therapy is considered. Individual tolerance to the drug must be determined by clinical observation and repeated blood counts. On the other hand, to be effective, repeated blood sulfanilamide determinations should be made in order to determine the correct dose for each patient and to make certain that adequate absorption is maintained during certain periods of time, as checked by proctoscopic examinations. As in diabetes and other chronic disorders these criteria can be established to best advantage by observation in a hospital at the start of the treatment. Too much emphasis cannot be placed on these factors because of the seriousness of the disease and the disability associated therewith, the long duration of the treatment at the patient's home, and the need for progress stool, proctoscopic, and roentgen examinations, regardless of the remission of symptoms, in order to appraise this form of therapy.

Conclusion

In view of our experience with 11 cases of chronic ulcerative colitis during the past year, in which a favorable initial response to sulfanilamide has been observed in eight cases, we believe this form of therapy should have a more thorough trial.

The difficulties in the appraisal of any single form of therapy in this serious disease have been emphasized.

Unless surgical indications are present at the time of the initial examination, we believe an adequate therapeutic trial with sulfanilamide should be included in the medical management of this disease, provided no contraindications to its use exist.

References

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