Treatment of Diversion Colitis by Short-Chain Fatty Acids

Prospective and Double-Blind Study

François Guillemot, M.D.,* Jean Frédéric Colombel, M.D.,* Christelle Neut, M.D.,† Nathalie Verplanck, M.D.,* Martine Lecomte, M.D.,‡ Claude Romond, M.D.,† Jean Claude Paris, M.D.,* Antoine Cortot, M.D.*

*From the * Clinique des Maladies de l'Appareil Digestif, Hôpital Claude Huriez, †Laboratoire de Bactériologie and ‡Laboratoire d'Anatomie Pathologique, Faculté de Pharmacie, Lille, France*

Diminished production of short-chain fatty acids (SCFA) by altered flora has been suggested in the pathogenesis of diversion colitis (DC). We evaluated prospectively the effectiveness of SCFA irrigation in 13 patients with excluded colon (eight males, five females; mean age, 48 years). The causes of diversion were inflammatory bowel disease (n = 4), colonic cancer (n = 2), sigmoid diverticulitis with perforation (n = 3), ischiorectal abscess (n = 2), and miscellaneous (n = 2). Patients were given, twice a day for 14 days in a double-blind manner, a 60-ml enema containing either SCFA (acetate: 60 mmol/liter; proprionate: 30 mmol/liter; and N-butyrate: 40 mmol/liter) (Group 1; n = 7) or isotonic NaCl (Group 2; n = 6). Endoscopy with biopsies was performed before starting the trial (D1) and 14 days later (D14). On D1 all patients had endoscopic and histologic findings suggestive of DC. No endoscopic or histologic changes were observed on D14 in either group. We conclude that endoscopic and histologic lesions of DC were not improved by SCFA irrigation during the 14 days. [Key words: Short-chain fatty acids; Diversion colitis]

Guillemot F, Colombel JF, Neut C, Verplanck N, Lecomte M, Romond C, Paris JC, Cortot A. Treatment of diversion colitis by short-chain fatty acids: prospective and double-blind study. Dis Colon Rectum 1991; 34:861–864.

Diversion colitis (DC) occurs after surgical diversion of the fecal stream. Clinical features (*i.e.*, cramping pains and bleeding) are well documented,[1] as are endoscopic changes (*i.e.*, erythema, friability, edema, nodularity, and aphthous ulcerations). Histologic changes include mucin granuloma and lymphoid follicle hyperplasia. However, the pathophysiology of such modifications remains unknown. Regression of clinical, endoscopic, and histologic features after reanastomosis suggests that a reduction of endoluminal nutrients—namely, short-chain fatty acids (SCFA), especially butyrate, which has been demonstrated to be the main nutrient of the colonocyte[2]—could play a role in the treatment of DC. SCFA are produced by anaerobic bacteria which are qualitatively and quantitatively reduced in human excluded colon.[3] Recently, disappearance of symptoms and of endoscopic and histologic changes after treatment of DC with SCFA irrigation has been reported in five patients in an open study.[4] The aim of the present study was to assess the effect of SCFA irrigation on endoscopic and histologic lesions of DC in a double-blind manner.

PATIENTS AND METHODS

Patients

Thirteen patients with DC (mean age, 43.7 years; eight males, five females) were studied. Clinical characteristics of patients are given in Table 1. All were ambulatory and had not taken any antibiotic medications for at least 4 weeks before study. None of the patients who had undergone surgical diversion because of Crohn's disease (CD) had clinical, endoscopic, or histologic evidence of recurrence at the time of the study. All had given their informed consent to the study, which was approved by the local ethical committee.

Methods

The patients underwent video sigmoidoscopy (Olympus JF.V.10) through the anal canal by the same endoscopist throughout the study. The scoring method of endoscopic changes was done according to Harig *et al.*[4] Each of five abnormalities—erythema, edema, friability, granularity, and erosions—was scored as absent (0), mild (1), or severe (2). The sum of endoscopic scores was made

A preliminary communication of this work was abstracted in Gut 1989;30:1470 and read at the meeting of the British Society of Gastroenterology, Dublin, Ireland, September 1989.
Address reprint requests to Dr. Guillemot: Clinique des Maladies de l'Appareil Digestif, Hôpital Claude Huriez, 1 Place de Verdun, 59037 Lille, France.

Table 1.
Clinical and Treatment Characteristics of 13 Patients with Diversion Colitis

Patient Number	Age (yr)	Sex	Reason for Diversion	Excluded Segment	Clinical Features	Months to Study	Treatment
1	57	M	Ischiorectal abscess	Sigmoid, rectum	None	24	SCFA
2	25	F	Crohn's disease	Transverse, left colon, sigmoid, rectum	None	29	SCFA
3	21	F	Crohn's disease	Sigmoid, rectum	Abdominal pain, occasional bleeding	2	NaCl
4	53	M	Sigmoid carcinoma	Sigmoid, rectum	None	18	NaCl
5	21	M	Crohn's disease	Transverse, left colon, sigmoid, rectum	None	3	SCFA
6	41	M	Cecum carcinoma	Entire colon	None	2	NaCl
7	50	M	Sigmoid diverticulitis with perforation	Sigmoid, rectum	None	32	SCFA
8	33	M	Sigmoid diverticulitis with perforation	Sigmoid, rectum	None	3	SCFA
9	53	M	Sigmoid diverticulitis with perforation	Sigmoid, rectum	None	2	SCFA
10	40	F	Crohn's disease	Sigmoid, rectum	None	2	NaCl
11	45	F	Ischiorectal abscess	Sigmoid, rectum	None	11	SCFA
12	79	F	Epiploic volvulus	Sigmoid, rectum	None	2	NaCl
13	50	M	Traumatic colic perforation	Transverse, left colon sigmoid, rectum	None	5	NaCl

with a range of 0–10. Two or three biopsies of the most inflamed areas were obtained by forceps biopsy and fixed in Bouin's solution. Histologic changes were evaluated on 1) surface erosions and exudate, 2) inflammation and edema of the lamina propria, 3) modification of crypt morphology, 4) presence of lymph follicles, and 5) mucin granulomas. Each modification was scored as 0 (absent), 1 (mild), or 2 (severe), and a global score was calculated by summing the items. The pathologist read the samples in a blinded manner. The same procedure was repeated at the start of the trial and 14 days later. The endoscopist and pathologist were blinded to the patient's treatment.

Treatment Protocol

Patients were randomized in two groups, those treated with SCFA (Group 1; n = 7) and those treated with isotonic saline solution (Group 2; n = 6). The SCFA solution was composed as previously described:[4] sodium acetate (60 mmol/liter), sodium proprionate (30 mmol/liter), and sodium N-butyrate (40 mmol/liter), with an osmolality of 280–290 mOsm/liter by addition of sodium chloride. pH was adjusted to 7 by titration of a molar sodium hydroxide solution. No antioxidants were added as preservatives. Patients were instructed on how to use the solution: 60 ml were instilled through a soft enema tip into the anus twice a day, the patient thereafter remaining supine for at least 30 min. Treatment was begun on day 1 (D1), after endoscopy.

RESULTS

Endoscopic and histologic data before and after treatment are given in Tables 2 and 3. On D1, all patients had endoscopic and histologic changes supporting the diagnosis of DC. All patients included on D1 were seen again on day 14 (D14). Patients' treatments are listed in Table 1. On D14, there were no endoscopic or histologic changes in either Group 1 or Group 2. No side effects were reported on D14.

DISCUSSION

SCFA are produced by colonic anaerobic fermentation. Among them, N-butyrate, which is the main SCFA into the colon, has been shown to have a trophic effect on the colonic epithelium and to increase regional blood flow and oxygen uptake.[5, 6] These findings led physicians to consider the possibility of treating DC with SCFA irrigation. Our results do not confirm those previously published

Table 2.
Individual Endoscopic and Histologic Scores Before (D1) and After (D14) Local Treatment in 13 Patients with Diversion Colitis

Patient Number	Type of Treatment	Endoscopic Score		Histologic Score	
		D1	D14	D1	D14
1	SCFA	7	7	1	1
2	SCFA	5	3	3	3
3	IS*	10	6	3	3
4	IS	6	6	3	3
5	SCFA	5	5	3	3
6	IS	2	3	2	2
7	SCFA	4	4	2	2
8	SCFA	2	1	3	1
9	SCFA	6	4	4	2
10	IS	5	4	5	5
11	SCFA	5	5	3	2
12	IS	2	1	2	1
13	IS	4	2	4	4

* IS = isotonic saline.

Table 3.
Endoscopic and Histologic Evaluation Before (D1) and After (D14) Local Treatment in 13 Patients with Diversion Colitis

	Endoscopic Evaluation	Histologic Evaluation	
Group 1 (n = 7)			
D1	4.9 ± 1.6	2.7 ± 0.9	
D14	4.1 ± 1.9	2.0 ± 0.8	NS
Group 2 (n = 6)			
D1	4.8 ± 3.0	3.2 ± 2.0	
D14	3.7 ± 2.1	3.0 ± 1.4	NS

Each patient received for 14 days an enema of either a SCFA solution (Group 1) or a saline solution (Group 2).
NS = not significant.

by Harig and Soergel.[7] In our prospective, double-blind trial, no improvement was detectable after SCFA irrigation as compared with isotonic sodium chloride.

Although our treatment protocol was similar to that of Harig and Soergel,[7] (same solution and administration), the duration of treatment was shorter in our study (2 weeks as opposed to 6 weeks). However, Harig and Soergel[7] pointed out that endoscopic and histologic improvement occurred after only 2 weeks in all their patients. Length of the excluded colon was more important in four patients of our study than in Harig and Soergel's study, in which all patients had undergone mucous fistula or rectosigmoid exclusion. Possible reflux of SCFA liquid irrigation beyond the sigmoid and splenic flexure could result in decreased concentration of SCFA in the rectosigmoid. However, 9 of the 13 patients in our study had only the sigmoid and rectum excluded, making such a hypothesis unlikely. Patients in Harig and Soergel's study had more severe clinical features and endoscopic lesions, averaging 9.25, as opposed to 4.9 in our study. However, the major aim of our study was to evaluate SCFA solution on endoscopic and histologic lesions, so endoscopic scores would have been decreased, even if initially lower, in our patients.

Etiology of diversion may be another reason for conflicting results. In our study, 4 of 13 patients had undergone surgical diversion because of CD. However, recurrence of CD was not supported by histologic features in those patients. Moreover, one patient in the addendum of Harig and Soergel's work also had a surgical diversion because of CD. Finally, concentrations of SCFA solution were determined according to Harig and Soergel; N-butyrate (the main nutrient of the colonocyte) was in excess in this preparation, as compared with its physiologic concentration in molar ratio to other SCFA. However, although the previous study and our study used an identical protocol, the total amount of SCFA infused over the whole day in our study was only 16 mmol, which may be insufficient. It may be valuable to test other concentrations or exclusive N-butyrate solutions in the treatment of DC. However, heterogeneity of bacterial populations in different types of excluded colon could, after all, explain such different results after SCFA enema in the treatment of DC. Further information, especially bacteriologic information, is needed for understanding such divergent results.

ACKNOWLEDGMENT

The authors thank Corinne Duthoit for skillful technical assistance.

REFERENCES

1. Glotzer DJ, Glick ME, Goldman H. Proctitis and colitis following diversion of the fecal stream. Gastroenterology 1981;80:438–41.
2. Roediger WE. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. Gut 1980;21:793–8.
3. Neut C, Colombel JF, Guillemot F, *et al.* Impaired bacterial flora in human excluded colon. Gut 1989;30:1094–8.

4. Harig JM, Soergel KH, Komorowski RA, Wood CM. Treatment of diversion colitis with short-chain-fatty acid irrigation. N Engl J Med 1989;320:23–8.
5. Whitehead RH, Young GP, Bhatal PS. Effects of short-chain-fatty acid on a new human colon carcinoma cell line (LIM 1215). Gut 1986;27:1457–63.
6. Kvietys PR, Granger DN. Effect of volatile fatty acids on blood flow and oxygen uptake by the dog colon. Gastroenterology 1981;80:962–9.
7. Harig JM, Soergel KH. Treatment of diversion colitis with short-chain-fatty acid irrigation. Gastroenterology 1987;92:1425A.