Digestive Diseases and Sciences, Vol. 36, No. 2 (February 1991), pp. 185–187

Rectal Irrigation with Short-Chain Fatty Acids for Distal Ulcerative Colitis

Preliminary Report

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Colon cells from patients with ulcerative colitis utilize short-chain fatty acids inefficiently and may be exposed to decreased concentrations of these compounds. To test whether irrigation of the inflamed mucosa with short-chain fatty acids is useful, we conducted a six-week preliminary trial in 12 patients with distal colitis. Each patient used twice daily rectal irrigations with 100 ml of a solution containing acetate (80 mM), propionate (30 mM), and butyrate (40 mM). Two patients stopped at three weeks, one because of no improvement and the other because of complete resolution of symptoms. Of the 10 who completed the trial, nine were judged to be at least much improved and showed a change in a mean disease activity index score from 7.9 ± 0.3 (SE) to 1.8 ± 0.6 (SE) ($P \leq 0.002$) and in a mucosal histology score from 7.7 ± 0.7 (SE) to 2.6 ± 0.7 (SE) ($P \leq 0.002$). Thus, ulcerative colitis patients appear to benefit from increased contact with or higher than usual levels of these critical energy substrates.

KEY WORDS: short-chain fatty acids; ulcerative colitis.

Short-chain fatty acids (SCFA) are the major energy source for colonic cells. Evidence that utilization of these compounds is impaired in ulcerative colitis (UC) suggests that diminished intracellular energy production may be important in the inflammatory process (1). Moreover, fecal water from patients with severe disease contains reduced concentrations of SCFA as well as markedly increased lactate at low pH, conditions which could be injurious to colonocytes (2, 3). These findings prompted us to test whether irrigating the colon with solutions designed to decrease lactate and/or increase luminal SCFA would prove useful in UC.

Manuscript received April 10, 1990; revised manuscript received August 27, 1990; accepted August 30, 1990.

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MATERIALS AND METHODS

We evaluated, in sequential trials: [1] a solution containing (in g/100 ml): sodium hydroxide 0.02, polyvinylpyrolodine, 0.71, *p*-hydroxybenzoic acid esters 0.1, and glycine 0.155, designed to raise pH and thereby shift endogenous bacterial production to SCFA rather than lactate (4); [2] a higher than normal concentration SCFA solution containing sodium propionate and sodium butyrate, 75 mM each, to try to improve uptake of SCFA rapidly; [3] a normal concentration SCFA solution containing sodium acetate (80 mM), sodium propionate (30 mM) (2), but twice-normal sodium butyrate (40 mM) because of its importance for colonic metabolism (4), adjusted to pH 7 with NaOH.

All patients had active UC, involving 15–65 cm of distal colon for at least three months, unresponsive to standard doses of sulfasalazine, rectal steroids, or

5-ASA. Those in the first two trials had also failed six weeks of oral prednisone and been off all medication except sulfasalazine for at least one month. In trial 3, the six patients on stable dosages of sulfasalazine (4 g/day), two of whom were also on a constant dose of prednisone (30 mg/day) for at least two months, without satisfactory control of symptoms, continued their same medication schedules; the other six took no medications during the trial.

The six patients in trial 1 and nine in trial 2 instilled 50 ml of the test solution twice daily for two weeks, while the 12 in the third trial instilled 100 ml of the "normal concentration" solution twice daily for six weeks. Protocols were approved by the human subject committees of the respective institutions, and all patients gave informed consent.

Clinical activity was evaluated by stool frequency, rectal bleeding, endoscopic appearance at flexible sigmoidoscopy, and impact of symptoms on activities of daily living (ADLs) using a scale from 0 (normal) to 3 (markedly abnormal) for each—a modified disease activity index (DAI) (5). Biopsies taken from the same area before and after the trial were graded on a similar 0–3 scale for each of the following criteria: cryptitis/abscesses, erosions/exudates, segmented leukocytes in the lamina propia, and glandular mucin depletion. The maximal score for either the clinical or histologic evaluation was 12. At the end of each trial, the DAI was recalculated, and the managing physician and patient assessed the global results of treatment as: unchanged, minimally improved, much improved, or complete remission. Pre- and posttreatment biopsies were evaluated by the study pathologist, who was unaware of the patient's condition.

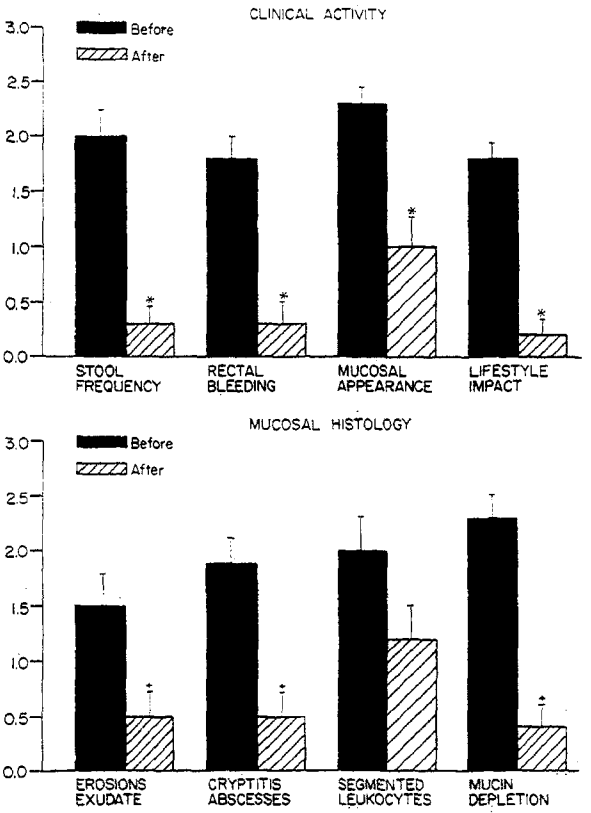

Fig 1. Clinical activity and mucosal histology component scores before and after short chain fatty acid rectal irrigation. Values are means ± SE for 10 patients. For disease activity index, * designates $P \leq 0.008$; for mucosal histology, † designates $P \leq 0.02$.

RESULTS

Trial 1. Four of the six patients completed the trial without noticeable variations in disease activity, while two required systemic steroids after 10 days due to worsening symptoms. Endoscopy and histology were unchanged in all.

Trial 2. All nine patients finished the two-week course. Although complete remission was never achieved, five showed clinical, four endoscopic, and three histologic improvement. Two-thirds improved in at least one parameter.

Trial 3. Twelve patients entered but two dropped out at three weeks, one because of lack of improvement and one who reported complete remission and wished no further investigations. Of the 10 who completed the six-week course, nine were at least "much improved" by global assessment. Changes in mean scores for individual components of the DAI are shown in Figure 1. Rectal bleeding stopped in eight, stool frequency became normal in seven, while the mucosal appearance as well as the impact on ADLs improved in all but one. The mean combined DAI improved from 7.9 ± 0.3 (SE) to 1.8 ± 0.6 (SE) ($P \leq 0.002$, sign test) (6). Mean scores for each component of the histology assessment also improved (Figure 1). Two patients became histologically normal, and three had a score of only one or two at the end. The mean combined histology score improved from 7.7 ± 0.7 (SE) to 2.6 ± 0.7 (SE) ($p \leqq 0.002$, sign test) (6). One patient's symptoms returned in a month, one after four months, and at the end of a year six patients remained well. Two patients were lost to follow-up.

DISCUSSION

Medical therapy of UC has changed relatively little in the last four decades. Our trial suggests that short-term rectal administration of a SCFA solution can induce clinical, endoscopic, and histologic improvement in some patients with distal UC. The results are especially promising since the patients studied were refractory to most standard medical

treatments. No side effects or toxicity were observed from SCFA rectal irrigation.

Failure of the alkalinizing solution may have been because the amount of buffer was insufficient or because exogenous buffers cannot induce endogenous conversion of lactate to SCFA. Trials 1 and 2 were brief, as no data were available about the advantages or possible side effects of intracolonic SCFA when the studies were designed. Even so, the partial improvement shown by most patients in trial 2 seemed promising. In the strikingly positive third trial, although the patients improved by three weeks, several showed accelerated responses between weeks 3 and 6. Reversion of mucosal histology to normal or near-normal in half the patients also suggests that six weeks may be adequate for a trial but does not define the ideal treatment course.

SCFA, products of anaerobic metabolism of carbohydrate by luminal bacteria, are the dominant ion species in the aqueous phase of feces (7). Their production prevents the osmotic cathartic effect of unaltered luminal carbohydrate, and during their rapid, concentration-dependent absorption, salt and water transport improves and bicarbonate appears, maintaining a neutral or alkaline colonic pH (8). Luminal SCFA, especially butyrate, serve as the major and preferred energy source for human colonocytes, especially those in the distal colon (4). They appear to have additional regulatory roles: in rats, SCFA instillation accelerates healing of colonic anastomoses and experimental colitis (9, 10); in the dog colon, they increase regional blood flow and oxygen uptake (11); and human colon cancer cell lines exposed to SCFA show a more normal cellular differentiation (12).

SCFA rectal irrigation promoted improvement in four patients with diversion colitis (13). In this condition, which has some similarity to UC, lack of SCFA appears to be the cause of the inflammatory process. Our patients with UC had mild to moderate colitis in which concentrations of SCFA are usually normal (3). Thus, their positive response is most consistent with the hypothesis that colitis colonocytes have impaired uptake or utilization of SCFA; the low concentrations in severe disease may only aggravate this preexisting metabolic defect. Our study design did not include an inert, neutral pH, control rectal irrigation. Therefore, our patients may have improved due to placebo effect or washout of offending substances such as lactate, which prevented response to prior therapies. However, our results strongly suggest the inflamed mucosa benefited from increased contact with SCFA, acting as critical energy substrates. We have begun a double-blind placebo-controlled trial to further define the therapeutic role of SCFA rectal irrigation in UC.

ACKNOWLEDGMENTS

This research was supported in part by a grant from the Dee and Moody Funds, Evanston Hospital, Evanston, Illinois. The authors wish to thank Margo A. Hinkle for her thoughtful review and help in preparation of this manuscript.

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