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Double-Blind, Placebo-Controlled Evaluation of 5-ASA Suppositories in Active Distal Proctitis and Measurement of Extent of Spread Using ^{99m}Tc-Labeled 5-ASA Suppositories

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Patients with active distal proctitis received either 5–aminosalicylic (5–ASA) acid or identical placebo suppositories, 500mg t.i.d. for 6 weeks. Activity at 3 and 6 wks was assessed using a Disease Activity Index (DAI), derived from four categories: number of daily evacuations more than usual, evacuations containing blood, sigmoidoscopy appearance, and physician's overall assessment. Each category was graded 0–3. There was thus 0–12 points scored ranging from complete remission to severe disease. A minimum score of 3 from two categories was necessary for study entry. Of 27 patients randomized, 14 received active medication and 13 placebo. Of the 14 patients, with initial mean DAI 7.1 ± 1.8, 11 were in complete remission at 6 wks (78.6%). Whereas, there was no significant change in the placebo group, with initial mean DAI 7.1 ± 1.8. An additional 6 patients with inflammatory bowel disease and 6 healthy volunteers were given ^{99m}Tc–labelled 5–aminosalicylic acid suppositories. The extent of spread was limited to the rectum, and the suppositories were retained for 3 hours. There was no absorbed radioactivity. 5–ASA suppositories are safe, well–tolerated, and effective treatment for active distal proctitis.

KEY WORDS: 5–aminosalicylic acid; distal proctitis; ^{99m}Tc–labelled 5–ASA; disease activity index.

Sulfasalazine has long been available as the mainstay of treatment of patients with inflammatory bowel disease (1). Sulfasalazine consists of two components: sulfapyridine and 5-aminosalicylic acid (5-ASA)—that are joined by a diazobond and are released when that bond is split in the colon by bacteria (2). Recent studies have shown that 5-ASA is the active component (3, 4), which both induces remission and may reduce the number of relapses in ulcerative colitis when given orally (5, 6). Sulfapyridine is the carrier molecule for 5-ASA and is likely responsible for the side effects and allergic reactions of sulfasalazine (7). 5-ASA is unstable in acid, is absorbed by the small intestine and, thus, needs ingenious pharmaceutical maneuvers to deliver 5-ASA to the distal small bowel and colon.

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5-ASA has been used topically in enema form for some years (3, 8–11). The enema had to be mixed immediately before use and was oxidized to a black compound. Currently, a stable preparation of 5-ASA is commercially available and is effective in treating distal colitis.

Distal proctitis is a subset of idiopathic ulcerative colitis; in it involvement of the distal colon is limited, being confined to the rectum in 25% of patients with additional sigmoid involvement occurring in another 29.5% (12). It presents usually as fresh rectal bleeding which is often intractable to conventional treatment with oral sulfasalazine, oral prednisone, or steroids applied topically to the rectum. This localized disease would be suitable for topical treatment with an effective agent that is easily applied to the area involved and, to reduce side effects, is not associated with any significant absorption. Such an agent is 5-ASA in suppository form.

We therefore compared the effect of 5-ASA suppositories with that of placebo suppositories in a prospective, randomized double-blind study in a series of patients with active distal proctitis. In addition, we measured the spread of rectal suppositories of ^{99m}Tc-labeled 5-ASA in another group of patients with inflammatory bowel disease and in healthy volunteers.

MATERIALS AND METHODS

Patients were admitted to the study with active distal proctitis involving the distal 15 cm or less on sigmoidoscopy. These patients were either unresponsive to standard therapy (sulfasalazine and/or oral prednisone or betamethasone enemas) or were newly referred patients. They had to be at least 18 years old, not pregnant, and without diverticulitis or a positive stool culture, and they must not have taken 4-ASA or 5-ASA within 48 hr, or rectal steroids within 14 days, of entry. Particular attention was paid to exclude patients with previous salicylate allergy, clinically significant liver or kidney dysfunction, and a history of previous bowel resection.

Patients were initially assessed by a physician and history and physical examination performed together with sigmoidoscopy and rectal biopsy. The presence of active bacterial infection was excluded by stool culture for *Salmonella, Shigella, Campylobacter, Yersinia,* and *Aeromonas*. Baseline hemogram, SMAC and urinalysis were performed; the patient was asked to keep a diary of daily symptoms; and the drug was dispensed in a double-blind fashion. Patients' response to treatment was formally assessed with a repeat evaluation, including sigmoidoscopy, at three and six weeks. Patients were contacted weekly by phone for symptom assessment, compliance, and side effects.

TABLE 1. DISEASE ACTIVITY INDEX

	*Disease activity index**			
	0	*1*	*2*	*3*
No. of daily evacuations more than usual	0	1–2	3–4	5+
Evacuations containing blood	none	occasional	most	all
Inflammatory mucosal changes on sigmoidoscopy	none	mild	moderate	severe
Physician's overall assessment of disease	none	mild	moderate	severe

*Range of possible total scores: 0–12.

Patients were also asked to keep a daily record of symptoms, ie, number of stools/day, degree of blood present, and to note the length of time the suppository was retained, up to 3 hr or more.

If the patient was taking oral sulfasalazine or oral prednisone, these were maintained in the same dose throughout the study period.

Objective assessment of the activity of the disease was assessed by means of a disease activity index (DAI), as detailed in Table 1.

If the patient was in remission, the DAI score was 0. Patients were admitted to the study with a score of 3 or greater, derived from at least two categories. The drug was supplied as 500 mg 5-ASA suppository or identical placebo, which was taken three times daily for six weeks.

An additional six patients with inflammatory bowel disease were offered a ^{99m}Tc-labeled 5-ASA suppository study, dose 1 mCi, and the results compared to those in six healthy volunteers. The stability of the compound was assessed by *in vitro* testing over time and *in vivo* testing with assessment of counts over the thyroid, parietal cells of the stomach, and accumulated counts excreted in urine over a 3-hr period.

The data were analyzed with group and paired *t*-testing and analysis of variance using a repeat measures design.

RESULTS

At the start of the study, there were five patients in the active group and seven in the placebo group taking no drugs; the other 15 patients had proctitis resistant to treatment, either sulfasalazine and/or oral prednisone, which were maintained at the same dose throughout the six-week study period.

There were 14 patients (eight men and six women, mean age 37.3 years ± 14.5 (1 SD) in the active group and 13 patients (nine men and four women, mean age 42.7 years ± 11.2) in the placebo group.

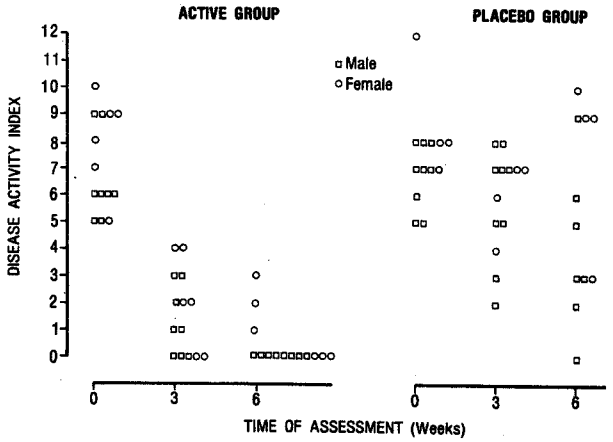

Fig 1. The disease activity index in all patients before and after treatment with 5-ASA suppositories or placebo suppositories.

There were two study failures, both of them were men in the placebo group; one dropped out at three weeks and one was found to have *Salmonella*. In six of 27 patients, this was the first episode of disease—none of these six dropped out. The mean duration of symptoms prior to this study was similar in men and women and in the two treatment groups at two to three months.

The difference between the initial mean DAI of the active group (7.1 ± 1.8) and that of the placebo group (7.4 ± 1.8) was not significant. At three weeks, the active group had a mean DAI of 1.6 ± 1.5, which was significantly lower than the pretreatment score ($P < 0.001$), whereas the placebo group had a mean DAI of 5.8 ± 1.9, which was not significantly different from the pretreatment value. At six weeks, the DAI in the active group was 0.4 ± 0.9 ($P < 0.001$). There was no increased statistical effect in the comparison of three weeks or six weeks versus the pretreatment values. In the placebo group, at six weeks the mean DAI was 5.4 ± 3.4 which was not significantly different from the pretreatment value.

In the active treatment group, only three patients failed to obtain a score of 0 at six weeks (Figure 1). All were women, two of whom were experiencing their first disease episode; only one had a DAI of 3. All three patients healed with continued treatment with 5-ASA suppositories. In the placebo group, one patient, a man, went into spontaneous remission at six weeks.

The mean DAI was higher in the females than men in both active (8.0 ± 1.8 vs 6.5 ± 1.6, $P = 0.006$) and placebo groups (8.7 ± 2.2 vs 6.7 ± 1.2, $P = 0.03$).

At entry the mean extent of active distal proctitis was no different in women than in men, either in the active treatment group (9.3 cm vs 9.6 cm) or in the placebo group (10.5 cm vs 9.3 cm).

There was no difference in response to treatment when the patients were considered as being on no coincident therapy or maintaining their usual drugs, sulfasalazine or prednisone.

No abnormal blood work was seen at three or six weeks in either the active or placebo groups. In particular, there was no change in renal function and urinalysis remained normal in all patients. No

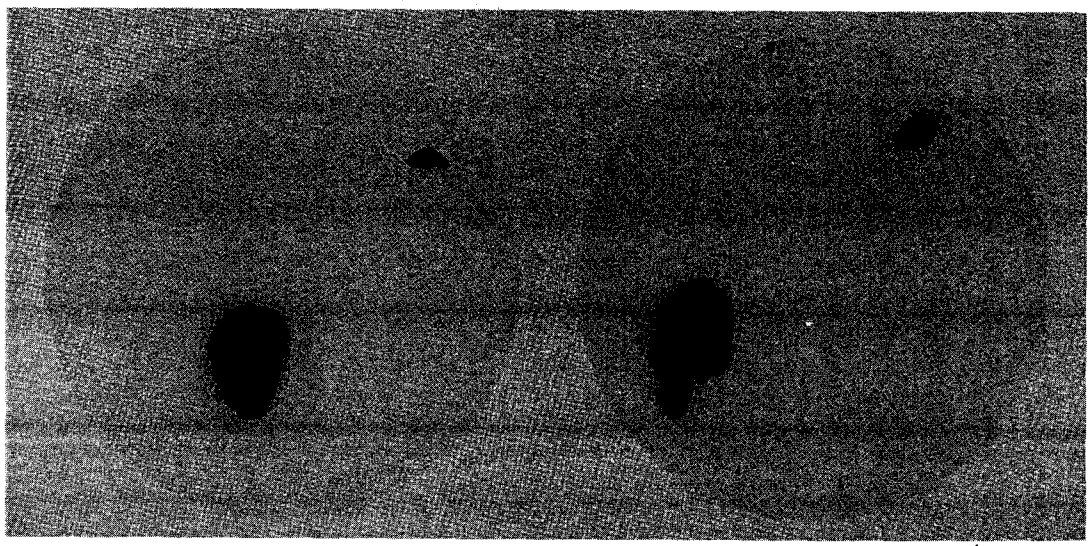

Fig 2. Anterior pelvic view in a healthy volunteer given a ^{99m}Tc-labeled 5-ASA suppository at 1 hr (left) and 3 hr (right).

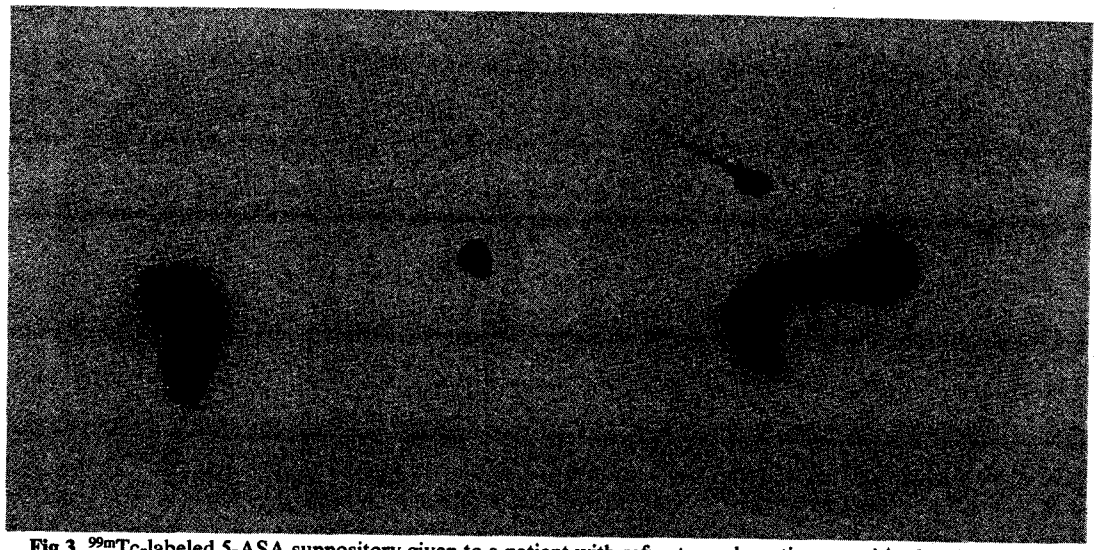

Fig 3. ^{99m}Tc-labeled 5-ASA suppository given to a patient with refractory ulcerative proctitis showing spread to the sigmoid colon at 3½ hr: anterior view (left) and lateral view (right).

side effects were recorded by the patients or investigators during this study.

The ^{99m}Tc-labeled 5-ASA suppositories remained localized to the rectum and sigmoid colon in all controls (Figure 2) and patients (Figure 3) studied. The preparation was stable; no radioactivity was detected over the thyroid or stomach in any patient or volunteer. Urine counts were barely above background.

DISCUSSION

There was a dramatic response to the use of 5-ASA suppositories, with patients regaining normal daily stools, losing their rectal bleeding, losing any symptoms of tenesmus or urgency, and tolerating and retaining the preparation extremely well. Indeed, most patients could retain the suppository for 3 hr or more, and none reported side effects. In addition, the medication was safe, no abnormal blood work being noted over the six-week period, and patient compliance was excellent.

As anticipated, the signs or symptoms in most patients taking placeboes for six weeks did not significantly change. The patients had had their symptoms for several weeks or months, with most having undergone previous treatment without success; thus, they tolerated with equanimity our six-week-long attempt to treat their illness with suppositories. Patients receiving placebo were offered active medication at the end of six weeks; all who accepted came into remission within six weeks.

It was of interest that half the women in the active group were not in total remission at six weeks, whereas all men were. The women had a mean initial DAI that was significantly higher than that of the men, which may help explain this finding. The extent of disease was similar in both groups.

Van Hees and coworkers (4) studied the effect of suppositories, sulfapyridine, 5-ASA, and placebo in 45 patients with proctitis. Each patient received two suppositories per day for four weeks. In 60% of patients given acetylated 5-ASA, total clinical remission occurred; the remission rate was 13% and 27% in patients given sulfapyridine or placebo.

Using the nonacetylated suppository, an increased dose, and increased duration of therapy, we had complete remission occur in 11 of 14 patients (78.6%) at six weeks

Labeling the 5-ASA suppositories with ^{99}Tc resulted in a stable compound which was confined to the rectum or adjacent sigmoid colon over 3 hr of the monitoring period. Thus, the 5-ASA suppository covers the inflamed area in these patients and was present in adequate contact with the inflamed mucosa to produce healing during this six-week period.

5-ASA suppositories are safe, well-tolerated, and are a very effective treatment for patients with distal proctitis. The treatment is equally effective as therapy

of first choice or in patients resistant to standard therapy with oral sulfasalazine and/or prednisone.

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