Mesalazine (5-Aminosalicylic Acid) Suppositories in the Treatment of Ulcerative Proctitis or Distal Proctosigmoiditis

A Randomized Controlled Trial

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A multicentre double-blind study was conducted to evaluate the efficacy and tolerability of 1 g or 1.5 g mesalazine daily compared with placebo in 94 patients with mild to moderate distal proctosigmoiditis (<20 cm). The study end point was the determination of clinical, endoscopic, and histologic remission rates at 4 weeks. Eleven patients, nine receiving placebo and two receiving 1.5 g mesalazine, withdrew during trial, mostly because of worsening of symptoms. At 4 weeks clinical remission was achieved in 7 of 31 (39%) patients with placebo, in 22 of 32 (69%) patients in the 1 g mesalazine group, and 23 of 31 (74%) patients in the 1.5 g mesalazine group. No serious clinical or biochemical side effect of treatment was reported. Mesalazine suppositories are safe, well tolerated, and very effective in patients with active distal proctosigmoiditis; 500 mg twice daily appears a suitable dose regimen.

Key words: 5-Aminosalicylic acid; distal proctosigmoiditis; drug therapy; mesalazine; randomized controlled trial; rectal treatment (suppositories); ulcerative colitis; ulcerative proctitis

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Topical treatment of ulcerative colitis was suggested about 30 years ago by Truelove, using a steroid derivative in distal ulcerative colitis (1). Since then, patients have mostly been treated either orally with drugs such as sulphasalazine or corticosteroids or topically, using steroids.

There has recently been renewed interest in topical treatment of ulcerative colitis as a result of a better understanding of the pharmacology of sulphasalazine (2) and controlled studies (3–5), which have suggested that 5-aminosalicylic acid (mesalazine) is the active moiety of sulphasalazine and that its therapeutic activity is very likely related to a topical action on the inflamed mucosa.

Ulcerative proctosigmoiditis is a relevant subset of idiopathic ulcerative colitis in which the disease process is limited to the rectum and the sigmoid colon. These forms are sometimes resistant to oral therapy but appear suitable for topical treatment with mesalazine, which is poorly absorbed in the colon (6).

Whereas enemas reach the splenic flexure (7) and constitute a very suitable approach for patients with left-sided disease (8), suppositories

have been shown to reach the sigmoid colon, and in fact are effective in patients with colitis confined to the rectosigmoid region (9). In addition, suppositories represent a more practical and suitable approach than enemas (10).

To determine the optimal dose regimen of mesalazine suppositories, we compared the efficacy and tolerability of two different doses of mesalazine suppositories with those of placebo in the treatment of active proctitis or distal proctosigmoiditis.

PATIENTS AND METHODS

Criteria for entry

The study population consisted of outpatients with active mild to moderate proctitis or proctosigmoiditis (11) with inflammation not beyond 20 cm from the anus on sigmoidoscopy. This diagnosis was confirmed by means of biopsy specimens taken from the areas of active disease.

Patients with first attacks or relapses of the disease were admitted to the study.

Patients were excluded if they were less than 18 or more than 75 years old, had systemic signs of disease, had shown previous salicylate allergy, or had received steroids for more than 7 days before entering the study. Pregnant or lactating women were also excluded.

Study design

Eleven Italian centres participated in this 4-week randomized, double-blind, placebo-controlled trial.

At entry, a physician examined the patients for history and performed a physical examination and a standardised assessment of colitis symptoms. A sigmoidoscopy with standard biopsy specimens taken 8–10 cm from the anal verge was then performed. A stool culture was done to exclude infectious colitis. Laboratory screening was performed before and after treatment and included the measurement of haemoglobin level, leucocyte count, serum creatinine value, serum alanine aminotransferase value, and urinalysis.

Patients were randomly assigned to one of three treatment groups. One group received mesalazine, 1.5 g/day; one received mesalazine, 1.0 g/day; and one group received placebo. In fact, each centre had received a definite series of packages, numbered consecutively. Each package contained the entire supply of the drug to treat one patient. The computerized randomization list used a block size of three. Daily supply of the drug was in a blister pack, each containing three suppositories, active and/or placebo in accordance with the treatment group. Patients were instructed to take one suppository three times daily for 4 weeks.

The study drug consisted of suppositories containing 500 mg mesalazine (Asacol®, Tillotts, U.K./Giuliani, Italy) and identical placebo suppositories, which contained only 3.0 g of a dispersing substance (solid semisynthetic glycerides with vegetable lecithin).

No rectal/oral steroids were allowed during the study.

Patients who enrolled for relapses occurring during oral maintenance treatment with sulphasalazine or mesalazine were allowed to continue to take the same dose throughout the study. Patients were clinically evaluated at 2 and 4 weeks, and a repeat sigmoidoscopy, with a biopsy specimen taken from the same area, was performed at 4 weeks.

Patients were asked to keep a daily record of symptoms (number and consistency of stools, presence of blood in the stool, rectal urgency, abdominal pain), of the time of retention of suppositories, and of possible side effects.

The number of stools/day was calculated as the average in the last 3 days before the visit. Rectal bleeding was defined as 0 = none; 1 (little) = streaks of blood; 2 (moderate) = obvious blood; 3 (much) = mostly blood in stools. Rectal urgency was defined as 0 = no; 1 = patient was able to postpone evacuation; 2 = only for short time; 3 = not able to postpone.

At the time of each clinical assessment the physician in charge was required to give a clinical evaluation of the patient status, both in absolute terms (remission) and in relation to the base-line conditions.

The endoscopic and histologic evaluation criteria were discussed and accepted for use by all investigators in the study.

Table I. Base-line data of patients

Variables	Placebo	Dosage of mesalazine, g/day	
		1	1.5
No. of patients	31	32	31
Male sex, no. (%)*	21 (68)	24 (75)	13 (42)*
Mean age (years) ±SD	41.2 ± 15.1	42.1 ± 14.1	37.1 ± 14.7
First attack, no. (%)	4 (13)	2 (6)	2 (6)
Duration of disease (years), mean ± SD	5.4 ± 8.4	4.6 ± 4.1	4.6 ± 4.2
Duration of current attack (days), mean ± SD	24.2 ± 22.2	22.8 ± 22.3	22.2 ± 19.7
Maintenance treatment, no. (%)	17 (55)	16 (50)	19 (61)
Extent of disease, no. (%)			
Proctitis	23 (74)	23 (72)	19 (61)
Distal proctosigmoiditis	8 (26)	9 (28)	12 (39)
Clinical activity, no. (%)			
Mild	18 (58)	14 (44)	13 (42)
Moderate	13 (42)	18 (56)	18 (58)
Endoscopy grades, no. (%)			
1	14 (45)	9 (28)	8 (26)
2	15 (48)	18 (56)	19 (61)
3	2 (7)	5 (16)	4 (13)
Histology grades, no. (%)			
1	8 (26)	4 (12)	6 (20)
2	14 (45)	13 (41)	15 (48)
3	9 (29)	15 (47)	10 (32)

* $P < 0.05$ compared with other groups.

The colonic appearance at endoscopy was assessed by the same physician at each centre, in accordance with Baron's criteria (12); 0 = normal mucosa; 1 (mild) = hyperaemic mucosa, indistinct vascular pattern; 2 (moderate) = friability, contact bleeding; 3 (severe) = spontaneous bleeding, ulceration, mucopurulent mucosa.

Histologic assessment of biopsy specimens taken during endoscopy was graded in accordance with the criteria of Truelove & Richard (13): 0 = normal; 1 = chronic inflammatory cell infiltrate in lamina propria; 2 = mild crypt injury with acute cell infiltrate, some crypt abscesses; 3 = marked crypt destruction with crypt abscesses and ulceration.

Patients were seen at 2 and 4 weeks, or at any other time if necessary.

Compliance was checked at the time of the visits by counting the number of unused suppositories.

End points for analysis included clinical, endoscopic, and histologic responses. The change in clinical, endoscopic, and histologic activity at 4 weeks was expressed as ordered variables (remission, improvement, unchanged, worse). A patient was considered in clinical remission when he/she was symptomless with no more than two bowel movements per day without visible blood in the stool. Clinical improvement was defined as a decrease in the severity of symptoms and signs, not meeting the criteria for remission. For the purposes of this study an improvement or deterioration of endoscopic and histologic activity was defined as a change of at least one grade.

Criteria for withdrawal from the trial at any time were intolerance to treatment, deterioration of symptoms, and the patient's request for any reason.

All patients had given informed consent in accordance with the Declaration of Helsinki. The study design was also approved by local ethical committees.

Table II. Clinical response at 4 weeks

	Placebo	Mesalazine suppositories	
		1.0 g	1.5 g
No. of patients	31	32	31
Remission	12 (39%)	22* (69%)	23* (74%)
Improvement	1 (3%)	4 (12%)	5 (16%)
No change	9 (29%)	5 (16%)	1 (3%)
Worse	0	1 (3%)	0
Withdrawals	9 (29%)	0	2 (6%)

* $P < 0.01$ versus placebo.

Remission rates:

	Observed difference	(95% confidence interval)
Mesalazine 1 g versus placebo:	30%	(7 to 54)
Mesalazine 1.5 g versus placebo:	35%	(12 to 59)
Mesalazine 1.5 g versus mesalazine 1 g:	5%	(−17 to 28)

Statistical considerations

For comparison of the treatment groups at base line, a one-way analysis of variance was used for continuous variables, and a chi-square test for nominal variables. Comparisons of proportions, such as the proportion of remission, were made by Fisher's exact test.

The Kruskal–Wallis test was used to compare ordered response variables among the three treatment groups, and the Wilcoxon rank sum test was used between two groups. All statistical tests were two-tailed and included all patients treated (intent-to-treat analysis). The 95% confidence intervals of the differences among response rates were also calculated.

Assuming an expected remission rate of 30% in the placebo group and a remission rate of 70% in either of the active treatment groups, we calculated that 30 patients per group were necessary to give the study a power of 90% with a type-I error of 5%.

RESULTS

Of the 94 patients admitted to the study, 32 received mesalazine, 1.0 g/day; 31 received mesalazine, 1.5 g/day; and 31 received placebo.

The treatment groups were comparable in terms of both patient demographic data and clinical features of the disease; only the 1.5-g group had a different sex distribution than the other groups ($p < 0.05$) (Table I).

Eleven patients (nine in the placebo group, two in the 1.5-g mesalazine group) stopped the treatment during the study, four in the first 2 weeks and five in the last 2 weeks. In the placebo group five patients withdrew because of worsening of symptoms, two because of lack of improvement, and one because of headache, and one was lost to follow-up study. In the 1.5-g mesalazine group one patient withdrew because of worsening of symptoms, and one was lost to follow-up study.

After 2 weeks 10 of 31 patients treated with placebo achieved clinical remission (23%) or showed improvement (10%), compared with 24 of 32 patients (remission, 41%; improvement, 34%) treated with 1 g mesalazine ($p < 0.05$) and 26 of 31 patients (remission, 45%; improvement, 39%) treated with 1.5 g mesalazine ($p < 0.01$, Wilcoxon rank sum test). No statistically significant difference was seen between the two mesalazine groups.

At 4 weeks clinical remission was observed in 12 (39%) patients in the placebo-treated groups and in 22 (69%) and 23 (74%) patients in the 1.0-g and 1.5-g mesalazine groups, respectively. The difference between either mesalazine group and placebo was statistically significant ($p < 0.01$, Fisher's exact test (Table II).

Table III. Results of treatment with 4-week mesalazine suppositories

	Endoscopic response			Histologic response		
		Mesalazine			Mesalazine	
	Placebo	1.0 g	1.5 g	Placebo	1.0 g*	1.5 g†
Remission	7 (23%)	19* (59%)	17* (55%)	2 (6%)	5 (16%)	3 (10%)
Improvement	5 (16%)	8 (25%)	9 (29%)	8 (26%)	18 (56%)	20 (65%)
No change	9 (29%)	4 (12%)	3 (10%)	12 (39%)	9 (28%)	6 (19%)
Worse	1 (3%)	1 (3%)	0	0	0	0
Withdrawal	9 (29%)	0	2 (6%)	9 (29%)	0	2 (6%)

* $p < 0.02$ versus placebo.
† $p < 0.01$ versus placebo.

The clinical response rate (remission or improvement) was slightly higher in the 1.5-g group than in the 1.0-g group, but the difference between the two dose regimens was not statistically significant.

Comparison of endoscopic responses (remission or improvement) showed differences between placebo and both mesalazine groups ($p < 0.02$), with similar results in the groups receiving active drug. Histologic changes were less dramatic than clinical or endoscopic changes. However, the comparison of the ordered response categories showed that both mesalazine dosages were significantly better than placebo ($p < 0.01$) (Table III).

There were no abnormal changes in any of the laboratory test results at the beginning and at the end of the trial period.

One patient receiving 1 g mesalazine developed transient facial erythema and mild fever not requiring discontinuation of the drug. No other side effects were reported. All patients retained the suppositories satisfactorily.

The count of unused suppositories showed that each patient had complied with the instructions given for the study.

DISCUSSION

There is good evidence from this study that 5-aminosalicylic acid (mesalazine) administered as suppositories represents an effective approach for patients with mild or moderate attacks of ulcerative proctitis or proctosigmoiditis extending not more than 20 cm from the anus; dose regimens of 500 mg twice daily and 500 mg 3 times daily both showed much better responses than placebo.

It should be emphasized that remission after 1 month was registered in 39% of patients treated with placebo, a value slightly higher than for others using placebo in distal ulcerative colitis. Van Hees et al. (4) found a remission rate of 27% in patients given placebo suppositories, and more recently, 29% of patients given placebo enemas were considered to be 'much improved' (14). It would thus appear that approximately one-third of patients with distal proctosigmoiditis respond favorably when treated with placebo by the rectal route and followed up carefully by a physician for 15–30 days.

However, the response rates obtained with both dosage regimens in this study were significantly better than those obtained with placebo at as early as 2 weeks. This difference continued to increase throughout the study period.

Our study found no statistically significant difference between the two dose regimens used. However, a clinical difference of 15% may exist but remain undetected owing to sample size used. Actually, to obtain a 95% chance of detecting a further clinical advantage of 15% (for example, 70% and 85%) in favor of the 1.5-g dose, more than 200 patients per treatment group would have been required. Nevertheless, owing to the excellent response of patients treated with the lower dose and to the small differences observed in

response rates between the two dose regimens, this trial provides enough evidence to establish that one 500-mg suppository administered twice daily is an adequate treatment regimen.

In all patients treated, suppositories dissolved completely, which would appear to be good evidence of an optimal ratio between mesalazine and the dispersing substance, which may contribute to healing the mucosa.

This study demonstrates that mesalazine suppositories are safe, well-tolerated, and very effective and confirms the value of topical mesalazine in the management of ulcerative proctitis or distal proctosigmoiditis.

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