Aliment Pharmacol Ther 1999; 13: 381–388.

A new mesalazine gel enema in the treatment of left-sided ulcerative colitis: a randomized controlled multicentre trial

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Accepted for publication 7 November 1998

SUMMARY

Background: A new mesalazine rectal gel preparation (without propellant gas) has been recently developed to improve topical treatment in distal ulcerative colitis.

Aim: To evaluate the efficacy, safety and patient tolerability of mesalazine gel enema compared with mesalazine foam enema in the treatment of patients with acute left-sided ulcerative colitis.

Methods: In a randomized multicentre investigator-blind parallel group trial, 103 patients with mild to moderate left-sided colitis or proctosigmoiditis were randomly allocated to mesalazine 2 g gel enema ($n = 50$ evaluable patients) and mesalazine 2 g foam enema ($n = 53$ evaluable patients) for 4 weeks. Clinical symptoms, endoscopic and histological findings were assessed at entry, 2 and 4 weeks. Patients' evaluation of treatment tolerability and acceptability was assessed at 2 and 4 weeks.

Results: After 4 weeks of treatment, clinical remission was achieved by 76% of mesalazine gel enema-treated patients and 69% of patients treated with mesalazine foam enema ($P = 0.608$). Endoscopic remission rates at week 4 were 51 and 52% for the mesalazine gel and foam enemas, respectively ($P = 0.925$). Histological remission was achieved by 30% of patients in both groups. Patients reported that the new mesalazine gel preparation was significantly better tolerated than the foam enema.

Patients in the foam group had significantly more difficulty in retention (25% vs. 6%, $P < 0.05$), abdominal bloating (50% vs. 26%, $P < 0.005$) and discomfort during administration (48% vs. 26%, $P < 0.05$).

Conclusion: The new mesalazine gel enema is efficacious and significantly better tolerated than the mesalazine foam enema.

INTRODUCTION

In recent years the rectal administration of mesalazine has become an established treatment for distal ulcerative colitis. This approach has been designed in order to ensure the delivery of large amounts of mesalazine to the distal colon, with low systemic absorption and a low incidence of side-effects.[1–3] Mesalazine solution, or foam enemas and suppositories are commercially available and widely used for the treatment of patients with proctosigmoiditis or distal ulcerative colitis and proctitis, respectively.[4–10]

Data on retrograde spread in the colon show that suppositories have a limited spread in the rectum and distal sigmoid colon,[11] while enema solutions have a greater, although highly variable, range capacity.[12, 13]

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In addition, solution enemas can be difficult to administer and have reduced patient compliance due to problems with retention.[10]

The foam enemas that are commercially available in Italy (Asacol foam, Giuliani & Bracco, Milan, Italy) offer a greater and more rapid capacity for retrograde distribution because of the generation of large volumes (120–200 mL) within the colon due to the addition of hydrocarbon propellants in the formulation.[14]

In order to further improve both tolerance and patient compliance to topical therapy, a new 60 mL single-dose high-viscosity mesalazine suspension (a thixotropic suspension) has recently been developed (Enterasin gel, Crinos S.p.A, Como, Italy).

The preparation is contained in a canister fitted with a valve. The spray system consists in a two-chamber device: an inner chamber (a flexible polyethylene-coated aluminium bag) containing the mesalazine suspension, and an outer chamber (an air-tight can) filled with pressurized nitrogen acting as a propellant. After activating the valve, the pressurized nitrogen squeezes the inner bag containing the suspension, which is released into the colon via a disposable rectal applicator.

The novelty of this device lies in the fact that the propellant gas is retained inside the can and is not delivered into the colon. In addition, the peculiar characteristics of the suspension are such that they permit an easy and complete release of the mesalazine suspension from the canister, as well as a better adhesion to the colonic mucosa. Furthermore, spreading is achieved more slowly and gradually compared to foam enemas.

The available data on retrograde spread in the colon show that the ready-to-use mesalazine gel enema displays a good spreading capacity, reaching the splenic flexure, with homogeneous distribution in the colon.[15]

This study was designed to compare the efficacy and safety of mesalazine gel enema with a commercially available mesalazine foam enema over a 4-week period of treatment of active proctosigmoiditis or colitis extending to the splenic flexure, and further to evaluate patient acceptance of both treatments.

METHODS

The study was a randomized, investigator-blind, parallel group trial conducted in patients attending out-patient clinics in nine Italian centres from October 1995 through to October 1996. The protocol was approved by the Ethics Committee or Internal Review Board of each participating centre and all patients gave informed, written consent.

Patients

Eligibility criteria included patients of either sex and aged 18–70 years, with clinical and endoscopically confirmed active mild to moderate proctosigmoiditis or ulcerative colitis extending to the splenic flexure. Patients were admitted into the study either in a state of clinical and endoscopic relapse or with first attacks of the disease and with negative stool cultures. At entry, they were required to have a minimum score of 3 on the 12-point Disease Activity Index (DAI).[4]

Patients were excluded if they had relapsed during treatment with rectal corticosteroid or rectal mesalazine preparations, if they had used oral corticosteroids or immunosuppressive drugs in the previous 3 months, they had Crohn's colitis, hypersensitivity to aminosalicylates, impaired liver and renal function, pregnancy or lactation.

Patients who were taking oral maintenance treatment with sulphasalazine or mesalazine at entry were allowed to continue, using the same dose throughout the study.

Treatment

All patients were randomly assigned to receive at bedtime, over a 4-week period, either 2 g mesalazine gel enema (Enterasin gel, Crinos S.p.A, Como, Italy) given rectally in one single application (total volume 60 mL) or 2 g mesalazine foam enema (Asacol foam, Giuliani & Bracco, Milan, Italy), given rectally as a single application (total volume $\approx$ 120 mL).

The drugs were packaged at a central location, and labelled and randomised in blocks of four according to a randomization list generated by a computer.[16]

Both treatments were presented as blank cylindrical aerosol cans with disposable applicators; however, the mesalazine foam can was half the size of the mesalazine gel cans. To preserve investigator blindness the endoscopist and the histopathologist were both blind to the type of treatment.

Trial assessments

At baseline, patients were examined clinically, endoscopically and histologically in order to confirm

diagnosis. The patients' demography, medical history, and concomitant medication were recorded. Once they had been randomised to either treatment, patients were asked to keep a daily record of symptoms (stool consistency and frequency, rectal bleeding, mucus and pus in stool, urgency, tenesmus, abdominal pain), the time of retention of gel enema or foam, as well as possible adverse events. These data were collected at each visit.

Clinical assessments of therapy were made at baseline, after 2 weeks (14 ± 3 days) and 4 weeks (28 ± 3 days) according to the 12-point Disease Activity Index (DAI)—measuring stool frequency, rectal bleeding, endoscopic findings, and physician's overall assessment of disease severity (Table 1).

Signs and symptoms such as mucus and pus in stools, abdominal pain, tenesmus and urgency were also recorded.

The endoscopic appearance of the colonic mucosa was assessed by the same physician in each centre, according to the criteria of Baron *et al.*[17] (Table 1).

Clinical and endoscopic remission were defined as a score of zero in the clinical and endoscopic portion of the DAI, respectively; an improvement in clinical and endoscopic activity was defined as a decrease in the severity of symptoms and mucosal inflammation (by at least one grade), respectively.

Histological disease activity was also assessed at study entry, and after 2 and 4 weeks, according to the criteria of Truelove & Richard.[18] Two biopsy specimens were taken 10 cm from the anal margin on the anterior rectal wall. The histological disease activity index score was determined by a single pathologists (G.B.) who was blinded to patient identification, clinical status and treatment, and was graded as follows: 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 ulcerations. Histological remission and histological improvement were defined as a histological disease score of zero or one, and a decrease in the histological disease index of one or two points, respectively.

At weeks 2 and 4 a Physicians Global Assessment (PGA) scale was used to assess changes in the disease state of each patient. This scale ranged from 1 to 6 and was determined by the physician's overall clinical assessment, based on patient symptoms, endoscope, and histological findings, as well as the patient's general well-being: 6 = much worse, 5 = minimally worse, 4 = no change, 3 = minimally improved, 2 = much improved, 1 = very much improved.

Safety was assessed by recording adverse events either observed by the investigator or reported by the patient at each follow-up visit.

At weeks 2 and 4, the patients were asked to express their opinion regarding the acceptability and tolerability of the formulations according to a questionnaire which assessed the following: difficulty of retention, discomfort during enema delivery, rectal pain, abdominal pain and abdominal bloating during enema administration, leakage. A two-point scale was adopted (0 = no problems at all, 1 = presence of problems).

Table 1. Disease Activity Index (DAI)

Stool frequency
0 = Normal number of stools for this patient
1 = 1–2 stools/day greater than normal
2 = 3–4 stools/day greater than normal
3 = 5 or more stools/day greater than normal
Rectal bleeding
0 = No blood seen in stool
1 = Streaks of blood with stools less than half the time
2 = Obvious blood with stools most of the time
3 = Blood alone passed
Mucosal appearance
0 = Normal mucosa or inactive disease
1 = Mild inflammatory changes (erythema, decreased vascular pattern; mild friability)
2 = Moderate inflammatory changes (marked erythema; absent vascular pattern; friability, erosions)
3 = Severe inflammatory changes (spontaneous bleeding, and ulcerations)
Physician's overall assessment of disease severity
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Maximum total score = 12

Statistical methods

The trial was designed to have an 80% power, with significance set at the 5% level. Using the end-point of patients' tolerability and acceptance of therapy, it was calculated that at least a total of 90 patients would be required in order to show that the mesalazine foam was 30% less well tolerated than the mesalazine gel.

A total of 103 patients were enrolled: 96 were included in the efficacy analysis, and 102 in the tolerability and acceptability analysis, according to a per protocol analysis.

The homogeneity of the groups was tested using a χ^2-test and Wilcoxon's rank sum test for qualitative variables, and Student's *t*-test for independent samples for the quantitative variable parameters.

Treatment efficacy and tolerability was verified by using a χ^2-test corrected for continuity. Scores from the DAI were analysed by nonparametric methods using ranks (Wilcoxon's rank sum test). Two-tailed tests of significance were applied throughout.

The 95% confidence limits for difference in rates between the treatment groups were also calculated.[19]

The analysis was performed using SAS statistical software and CIA (Confidence Interval Analysis) computer programs.[20]

RESULTS

One hundred and three patients entered the study; 50 received mesalazine gel and 53 mesalazine foam. Seven patients (one in the mesalazine gel group and six in the mesalazine foam group) were excluded from the efficacy analysis; four because of incorrect entry criteria, two discontinued treatment after only a few days and failed to keep further appointments and one was noncompliant (Table 2).

A further 11 patients (eight in the mesalazine gel group and three in the mesalazine foam group) were excluded from the histological analysis because of histology in remission at entry. However, this patient group was included in the clinical and endoscopic analysis because they had an initial DAI score in the range from 3 to 8: one patient in the mesalazine gel group had a DAI score of 3, four patients (three in the mesalazine gel group and one in the mesalazine foam group) had a DAI of 4, two patients (each in the mesalazine gel and foam group) had a DAI score of 5, two patients in the mesalazine gel group had a DAI score of 6, and two patients, one in the mesalazine foam group and one in the gel group, had DAI scores of 7 and 8, respectively.

Ninety-six patients (49 in the mesalazine gel group and 47 in the foam group) were included in the clinical and endoscopic analysis population and 85 (41 in the mesalazine gel group and 44 in the foam) in the histological assessment.

One hundred and two patients (50 in the mesalazine gel group and 52 in the foam group) were included in the tolerability/acceptability evaluation.

Five patients in the mesalazine foam group withdrew during the trial: four because of lack of improvement, one because of poor compliance.

Characteristics of the two treatment groups are presented in Table 3 and were comparable with regard

Table 2. Data sets analysed

	No. of patients	
	5-ASA gel	5-ASA foam
Randomized	50	53
Non-compliance	0	1
Tolerability analysis	50	52
Protocol violation (entry)	1	3
Lost to follow-up	0	2
Clinical and endoscopic analysis	49	47
Histology in remission (entry)	8	3
Histological analysis	41	44

Table 3. Baseline entry characteristics

	5-ASA gel (n = 50)	5-ASA foam (n = 53)
Sex (%)		
Male	36 (72)	30 (57)
Female	14 (28)	23 (43)
Age (years) mean (s.d.)	42.2 (12.7)	37.4 (12.4)
Duration of disease (years)		
Mean (s.d.)	5.9 (5.0)	5.8 (5.5)
Range	0.3–20	0.25–31
Extent of disease (%)		
Proctosigmoiditis	38 (76)	36 (68)
Left-sided colitis	12 (24)	17 (32)
Concomitant oral 5-ASA/SSZ (%)	40 (80)	36 (68)
Initial DAI score		
Mean (s.d.)	6.12 (1.88)	6.19 (1.55)
Range	3–11	4–10
Endoscopy score		
Grade 1	9	6
Grade 2	39	41
Grade 3	2	5
Not available	—	1
Histology score		
Grade 1	9	6
Grade 2	19	22
Grade 3	22	24
Not available	—	1

Table 4. Mean values (s.d.) of DAI score at baseline and weeks 2 and 4

	Baseline	Week 2	Week 4
5-ASA gel	6.12 (1.88)	2.36 (2.32)*	1.44 (2.18)*
95% CI	5.57–6.66	1.69–3.03	0.82–2.07
5-ASA foam	6.19 (1.55)	2.82 (2.24)*	1.57 (2.29)*
95% CI	5.73–6.64	2.16–3.49	0.85–2.28

* $P < 0.001$ in comparison to baseline

to extent of disease, grade of endoscopic or histological score, and number of patients with oral maintenance therapy.

Efficacy assessments

Both treatments significantly reduced the mean total DAI scores from baseline (Table 4). After 2 and 4 weeks, the mean DAI score declined by 3.76 and 4.68, respectively for patients receiving mesalazine gel, and by 3.37 and 4.62 in the mesalazine foam group. There were no significant differences between treatments ($P = 0.22$ and $P = 0.92$, respectively), but both treatments significantly decreased the scores ($P < 0.001$ at 2 and 4 weeks).

Table 5 shows the clinical, endoscopic and histological rate of remission, improvement and failure at 2 and 4 weeks of treatment.

Both treatments produced a significant improvement from baseline in all symptoms. In the group treated with gel, 17 of 49 (35%) were in clinical remission after 2 weeks compared with 19 of 47 (40%) treated with foam. Four patients in the foam group discontinued the study at week 2 following inadequate response. After 4 weeks, 37 of 49 (76%) in the gel group and 29 of 42 (69%) in the foam group were in remission. No statistical differences were observed between treatments.

The endoscopic appearances showed a significant improvement after both treatments. In the group treated with the gel, 14 of 49 (29%) were in endoscopic remission after 2 weeks, compared with seven of 47 (15%) in the foam group ($P = 0.120$). After 4 weeks, 25 of 49 (51%) in the gel group and 22 of 42 (52%) in the foam group were in remission, with no statistical difference between treatments.

In addition, there was no statistically significant difference between treatment groups in terms of histological response.

Physicians Global Assessment scores also indicated progressive improvement in both groups (Figure 1). At week 2 there was a slightly greater frequency of 'very much' improvement in the mesalazine gel group than in the foam group. However, the difference between treatments in PGA scores was not significant at any time.

Table 5. Clinical, endoscopic and histological results

	Week 2			Week 4		
	5-ASA gel	5-ASA foam	*P*-value	5-ASA gel	5-ASA foam	*P*-value
Clinical symptoms						
Remission	17 (35%)	19 (40%)		37 (76%)	29 (69%)	
Improvement	30 (61%)	23 (49%)	0.320	9 (18%)	8 (19%)	0.608
Failure	2 (4%)	5 (11%)		3 (6%)	5 (12%)	
Endoscopy						
Remission	14 (29%)	7 (15%)		25 (51%)	22 (52%)	
Improvement	25 (51%)	23 (49%)	0.120	18 (37%)	14 (34%)	0.925
Failure	10 (20%)	17 (36%)		6 (12%)	6 (14%)	
No. of patients	49	47		49	42	
Histology						
Remission	8 (20%)	9 (21%)		12 (30%)	12 (30%)	
Improvement	17 (41%)	16 (37%)	0.931	18 (45%)	20 (50%)	0.756
Failure	16 (39%)	18 (42%)		10 (25%)	8 (20%)	
No. of patients	41	43		40	40	

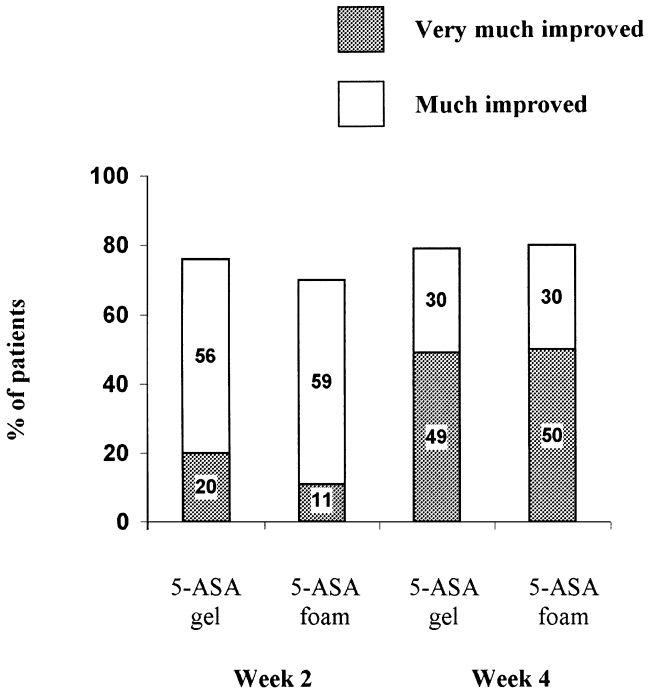

Figure 1. Physician's Global Assessment scoring.

Safety assessments

Adverse events. Two patients receiving mesalazine gel enemas and one patient taking foam enemas developed, respectively, self limiting renal colic, insomnia and skin eruption which were not thought to be related to the trial medications.

Patient evaluation of therapy. The analysis of the data collected showed that the mesalazine gel enema was significantly better tolerated than the mesalazine foam (Table 6).

The most common problems reported by patients during mesalazine foam treatment administration were: difficulty in retention, abdominal bloating and discomfort during administration.

After 2 weeks, the mesalazine foam patients had significantly more difficulty in retention, abdominal bloating and discomfort during administration (37, 56 and 58%, respectively), compared to the mesalazine gel group (4, 18 and 18%, respectively) ($P < 0.001$). After 4 weeks, the percentage of patients with difficulty in retention, abdominal bloating and discomfort during administration was 25, 50 and 48% in mesalazine foam group and 6, 26 and 26%, respectively, in the gel group ($P < 0.005$).

DISCUSSION

The present study was designed to evaluate the efficacy and patient acceptability and tolerability of a new 5-ASA gel preparation, in comparison to that of 5-ASA foams in patients with left-sided ulcerative colitis. Although the enemas were not identical in appearance, they were only labelled with a trial number, and every attempt was made to ensure the investigator blinding. Endosopic and histological assessments were carried out without the knowledge of the patient group.

After 4 weeks there were significant improvements in symptoms as well as in endoscopic and histological grades, that were of a similar degree in both treatment groups. Data regarding the patients' acceptability and tolerability showed that the new 5-ASA gel enema was significantly better tolerated by the patients because it was easier to retain and caused significantly less discomfort, abdominal pain and abdominal bloating.

Significant differences between the two groups in the results from the tolerability questionnaire were found at both 2 and 4 weeks of treatment. However, at 2 weeks a significantly greater proportion of patients reported no problems at all in using 5-ASA gel compared with the foam, suggesting that the new formulation is better

Table 6. Patient evaluation of tolerability and acceptability of therapy

	Week 2			Week 4		
	5-ASA gel (n = 50)	5-ASA foam (n = 52)	Difference (95%)	5-ASA gel (n = 50)	5-ASA foam (n = 44)	Difference (95%)
Difficulty in retention	2 (4%)**	19 (37%)	33% (19–47)	3 (6%)*	11 (25%)	19% (5–33)
Abdominal bloating	9 (18%)**	29 (56%)	38% (21–55)	13 (26%)*	22(50%)	24% (5–43)
Discomfort during administration	9 (18%)**	30 (58%)	40% (23–57)	13 (26%)*	21 (48%)	22% (3–41)

*$P < 0.05$, ** $P < 0.001$, in comparison with 5-ASA foam (χ^2; Yates correction).

accepted in the initial phases of the disease when activity is more pronounced.

The better tolerability of the 5-ASA gel is most likely to be linked to its innovative formulation (a thixotropic suspension) and release system, which does not deliver the propellant gas into the colon, and permits an easy and complete release of the active ingredient, together with a better adhesion and homogeneous distribution to the colonic mucosa.

The topical treatment of distal colitis makes it possible to administer a high dosage of the active drug directly to the inflamed mucosa, as well as achieving a low level of systemic absorption. Rectal formulations of 5-ASA represent the first choice treatment for distal colitis, being significantly superior both to placebo and topical corticosteroids, as has been confirmed by two recent meta-analyses.[7, 8]

Mesalazine suppositories are thought to be the best treatment for patients with proctitis,[9, 21] while liquid enemas and foams, thanks to their retrograde spread, are suitable for more extensive disease.[12, 13] Mesalazine foam enemas have been shown to be superior to prednisolone foam enemas,[22] and have a more uniform distribution as well as a greater persistence than the liquid enema in the descending and sigmoid colon.[15] Moreover, when mesalazine foam enemas were given in equal doses, they gave a faster remission compared with mesalazine liquid enemas, and patient evaluation of the therapy showed that the foam was more comfortable, more practical, easier to retain, and interfered less with daily living.[10]

The extent of spread of the mesalazine gel enema used in this study has been investigated and was found to reach repeatably into the splenic flexure, with a homogeneous distribution into the left colon. In addition, the systemic absorption of the new gel enema was found to be similar to that of other mesalazine topical preparations on the market.[15]

We conclude that the new mesalazine gel enema is a highly efficacious and safe preparation and that it is better tolerated than the mesalazine foam enema. This technological advance should help with patients compliance to topical treatment.

ACKNOWLEDGEMENTS

We are grateful for financial and technical support given by Crinos S.p.A, Piazza XX Settembre 2, 22079 Villa Guardia, Como, Italy.

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