Aliment Pharmacol Ther 1997; 11: 335–340.

Efficacy and tolerance of mesalazine suppositories vs. hydrocortisone foam in proctitis

D. LUCIDARME*, P. MARTEAU†‡, M. FOUCAULT†, B. VAUTRIN† & B. FILOCHE*
* *Hôpital Saint-Philibert, 59160 Lomme, France;* † *Ferring SA, Gentilly, France; and* ‡ *Hôpital Saint-Lazare, Paris, France*

Accepted for publication 2 October 1996

SUMMARY

Background: Topical treatments with steroids or mesalazine are the most effective treatments for idiopathic proctitis.
Aim: to compare the efficacy and tolerance of mesalazine suppositories vs. hydrocortisone acetate foam in the treatment of acute proctitis.
Patients and methods: 242 patients with active idiopathic proctitis were randomized to receive once daily either one Pentasa suppository (mesalazine 1 g) or 100 mg hydrocortisone (Colofoam) for 14–21 days (until remission). Disease activity and tolerance of the treatments were assessed using a daily questionnaire, by physician assessment, and endoscopy score.
Results: Both treatments induced a significant reduction in disease activity. Mesalazine suppositories were significantly more effective than hydrocortisone on rectal blood loss ($P = 0.002$) and mucus ($P = 0.02$) parameters, and on the degree of the decrease in endoscopy score ($P = 0.02$). No significant difference was observed between treatments concerning histology or tolerance.
Conclusion: Mesalazine suppositories were as well-tolerated as hydrocortisone foam, but were more effective for some parameters of disease activity.

INTRODUCTION

The efficacy of topical treatment with enemas, foams, and suppositories of mesalazine and steroids is well established in the treatment of mild or moderate episodes of idiopathic proctitis. Are there differences in their efficacy and tolerance?, and which should be chosen as a first line treatment? Seven studies have compared the efficacy of mesalazine enemas and topical steroids. A significantly better efficacy of mesalazine enemas has been observed in six of them,[1–7] the last study showing no difference between 3 g mesalazine and 30 mg prednisolone phosphate sodium enemas after 28 day treatment.[7] Foams and suppositories are often preferred by patients to enemas.[8–10] One study compared the efficacy of mesalazine foam and prednisolone foam, and showed that mesalazine was significantly more efficient.[11] Until now, only one study had compared the efficacy and tolerance of mesalazine suppositories and a rectal steroid foam in subjects with proctitis or rectosigmoiditis.[12] The patients were treated twice daily for 4 weeks with 500 mg mesalazine suppositories or 178 mg of hydrocortisone foam. The authors reported a better effect of mesalazine in patients with proctitis, and a better compliance in the same group. Pentasa suppositories have been developed to slowly deliver mesalazine from microgranules so that only a single application per day is necessary.[13] In a recent trial their efficacy appeared superior to that of 500 mg twice a day of classical glycerine mesalazine suppositories.[14] The aim of this randomized study was to compare the efficacy and tolerance of 1 g Pentasa suppositories and a rectal hydrocortisone foam (Colofoam) in patients with active idiopathic proctitis.

Correspondence to: Prof. B. Filoche, Hôpital Saint-Philibert, 59160 Lomme, France.

PATIENTS AND METHODS

Patients

The study was performed in adult out-patients presenting with active idiopathic proctitis. Inclusion criteria were the presence of a biopsy proven active idiopathic proctitis which did not spread beyond the recto-sigmoid junction,

endoscopy score of 2–4, body temperature less than 38 °C, blood white cell counts less than 12×10^9/L, ESR less than 40 mm, serum CRP less than three times the upper limit of the normal value. The endoscopy lesions were scored for severity as follows: score 0, normal mucosa erythaema; score 1, granularity or oedema or lack of the normal vascular pattern; score 2, contact bleeding; score 3, spontaneous bleeding; score 4, superficial ulcerations; score 5, deep ulcers.[13] Patients receiving long-term oral maintenance treatment for ulcerative colitis were included if there had been no change in their treatment during the last 14 days before inclusion, and no change was judged to be necessary during the trial. Patients treated with any rectally instilled drug during the last 14 days were excluded. Exclusion criteria were age above 75 years or below 18, proctitis from another origin (infectious, parasitic, radiotherapy, post-colectomy), extrarectal localization of Crohn's disease or ulcerative colitis, hypersensitivity to salicylates, contra-indication to steroids, use of anticoagulant or oral steroids, pregnancy, breast feeding, and failure of a previous treatment with mesalazine or hydrocortisone foam.

Study protocol

The study was a randomized, open, parallel group multicentre trial with 35 centres in the Nord Pas-de-Calais area.

Patients were included after evaluation of the initial clinical, endoscopic and histological activity on a rectal biopsy sample. The following scale was used for histological grading: score 0: normal mucosa; score 1: chronic infiltration of the lamina propria with lymphocytes or plasma cells without acute inflammation (rare polymorphonuclears) and no architectural disorder; score 2: irregular crypts and/or acute inflammatory cell infiltrate and/or a few crypt abscesses; score 3: extensive crypt injury with numerous crypt abscesses and/or ulceration.

Treatment consisted of one administration per day, at bed-time, of either a 1 g mesalazine suppository (Pentasa, Ferring, Copenhaguen, Denmark) or a dose of rectal foam delivering 100 mg hydrocortisone (Colofoam, Stafford Miller, Plymouth, UK). Treatment was given for 14 days in every patient, and was stopped at day 14 when the following criteria for remission were met: absence of nocturnal emission, absence of blood in stools, no more than two mucus evacuations per day and an endoscopic score of 0 or 1. If remission was not obtained at day 14, treatment was continued for one more week, and a new clinical and endoscopic evaluation was performed at day 21.

Patients reported on a diary card the following signs: number of bowel movements per day, presence of blood in stools, number of mucus evacuations, adverse events, and early rejection of the suppositories. The clinical and endoscopic activities were evaluated at day 1, day 14 (and eventually at day 21) by the same physician. The following parameters were recorded: number of bowel movements per day, presence of blood in stools, mucus, presence and intensity of tenesmus and abdominal pain, and adverse events. Abdominal pain was graded on a scale from 0 (no pain) to 3 (severe). Physician global assessment consisted of worsening, stable, moderate improvement, important improvement, remission. Blood cell counts, ESR and CRP were measured at entry.

End-points

The major outcome criteria were efficacy for the clinical symptoms quoted on the daily questionnaire and at the physician assessment at day 14. Secondary outcome criteria were the endoscopy score, the degree of its decrease from day 0 to day 14, and the physician global assessment. Tolerance was assessed by recording premature dropouts, the declaration of potential adverse events and questionnaires completed by the patients.

Statistical analyses

To show a 20% difference in the efficacy of the treatments with a β risk of 0.1, 122 subjects had to be included in each group.

Results are expressed as means with their standard errors. The main analysis was on an intention-to-treat basis and included all randomized patients. The non-parametric Mann–Whitney test was used to compare quantitative or ordinal variables. The χ^2 test was used to compare qualitative variables. The Mantel–Haenszel adjustment method was used to analyse the efficacy of treatment on clinical symptoms taking into account the initial endoscopy score and a potential oral associated treatment.

Ethics

The study protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche

Médicale du Centre Hospitalier Général de Valenciennes–Région Nord Pas-de-Calais. All volunteers gave written informed consent to the protocol.

RESULTS

Two hundred and forty-two patients were included for 250 episodes of acute idiopathic proctitis (132 in the mesalazine group, 118 in the hydrocortisone group) from September 1992 through July 1994. Eight patients were included twice because of two episodes of acute proctitis which were separated by 38–488 days. Groups did not differ for age, sex, weight, diagnosis, duration of the episode, severity of symptoms and endoscopy scores, associated oral treatment, ESR, CRP or white blood cell counts (Table 1). More subjects in the mesalazine group had suffered from previous episodes of proctitis (Table 1) but no difference was noted in the number of subjects having an episode of active proctitis in the year before inclusion (37% vs. 28% for the mesalazine and hydrocortisone groups, respectively, $P = 0.12$). Blood platelet counts were slightly higher in the mesalazine group (Table 1). Twenty patients stopped the treatment (10 in each group); this included six cases of intolerance in the mesalazine group and three in the hydrocortisone group. Eighty patients (45 in the mesalazine group, 35 in the hydrocortisone group) were not in remission at day 14 and followed the treatment until day 21.

Treatment with mesalazine suppositories and hydrocortisone foam both resulted in a significant improvement in clinical symptoms and lesions.

Clinical symptoms

The efficacy of both treatments on the number of stools per day did not differ significantly (Table 2). The

Table 1. Characteristics of the patients (mean ± S.E.M.)

	Mesalazine suppository	Hydrocortisone foam	*P*
No. randomized	132	118	
Age (years)	39 ± 3.6	41 ± 4.0	0.60
Males (%)	55.3	53.4	0.76
Weight (kg)	65.8 ± 3.6	67.2 ± 3.4	0.28
Previous episodes (%)	62.1	47.0	0.02
Duration of current exacerbation (days)	75 ± 14	98 ± 19	0.92
Ulcerative colitis (%)	47	50	0.88
Crohn's disease (%)	3.8	3.4	
Patients with oral treatment (%)	20.5	19.5	
ESR (mm/h)	10.8 ± 12.0	9.2 ± 10.3	0.08
CRP (mg/L)	6.1 ± 10.3	4.6 ± 5.9	0.40
Leucocytes ($\times 10^9$/L)	7.2 ± 1.8	7.5 ± 2.1	0.21
Platelets ($\times 10^9$/L)	312 ± 102	273 ± 77	0.08
Lost to follow up (*n*)	4	3	
Protocol violation (*n*)	7	6	

Table 2. Clinical symptoms recorded at consultations at day 1 and day 14 in patients receiving mesalazine suppositories or hydrocortisone foam to treat an acute episode of idiopathic proctitis

	Mesalazine suppository	Hydrocortisone foam	*P*
No. of stools per day			
at entry	3.7	3.6	0.37
after 14 days	2.1	2.3	0.06
Blood in stools (% of the subjects)			
at entry	85.6	88.4	0.52
after 14 days	22.1	40.2	0.004
Mucus (% of the subjects)			
at entry	66.4	74.5	0.79
after 14 days	22.1	36.4	0.02
Tenesmus or abdominal pain (%)			
at entry	70.2	62.2	0.44
after 14 days	22.1	27.1	0.39

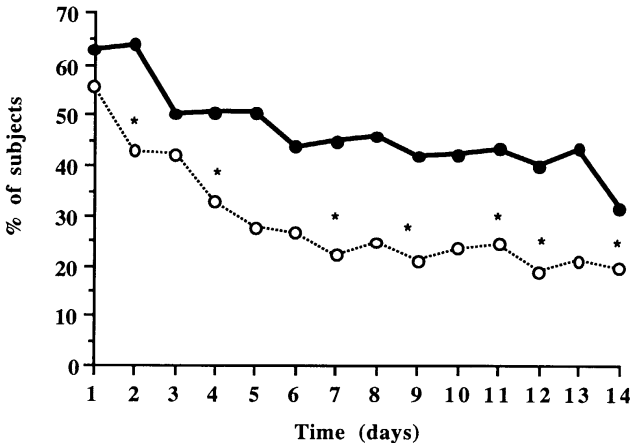

Figure 1. Presence of blood in stools during the first 14 days of treatment as reported on the diaries for the patients treated with mesalazine suppositories (white circles) or hydrocortisone foam (black circles). $^{*}P < 0.05$.

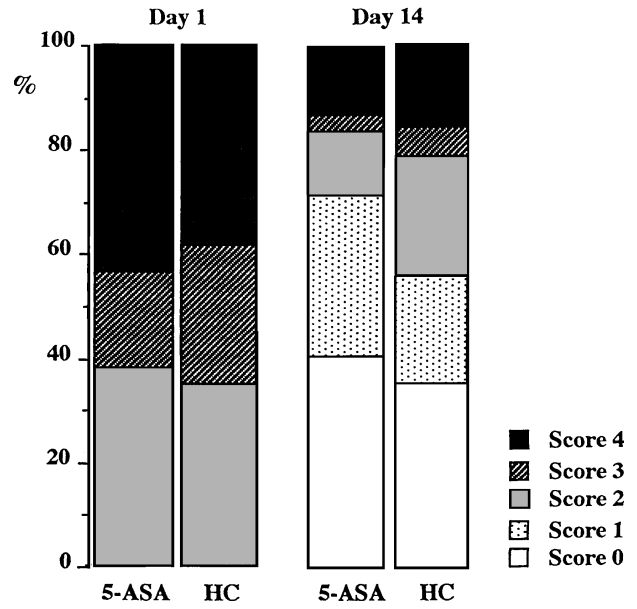

Figure 2. Mean endoscopy scores in the patients receiving mesalazine suppositories or hydrocortisone foam at day 1 and day 14. (Score 0 = normal mucosa erythaema; score 1 = granularity or oedema or lack of the normal vascular pattern; score 2 = contact bleeding; score 3 = spontaneous bleeding; score 4 = superficial ulcerations.[13])

disappearance of blood in stools was significantly more pronounced in the mesalazine group (Table 2, Figure 1). The difference was significant as early as day 2 (43% vs. 64% for mesalazine and hydrocortisone, respectively). At the last evaluation, the proportion of patients without blood in stools were 84.2% in the mesalazine group vs. 62.1% in the hydrocortisone group ($P < 0.001$). The presence of mucus in stools was also significantly different between the two treatments (Table 2): at the last evaluation, the numbers of patients without mucus in stools were: 83% vs. 64% for mesalazine and hydrocortisone, respectively ($P = 0.004$). Presence and intensity of tenesmus and abdominal pain did not differ significantly between groups (Table 2).

Endoscopy, histology, physician global assessment

No significant differences between groups were observed concerning endoscopy scores at days 14 and 21 (Figure 2) ($P = 0.09$ at day 14; $P = 0.21$ at day 21). When expressed as the decrease in endoscopy score, the improvement was significantly more pronounced in the mesalazine group ($P = 0.02$). A decrease of 2 or more points on the endoscopy scale was noticed in 38% and 24% in the mesalazine and hydrocortisone foam groups, respectively, and a decrease of 3 or more points on the endoscopy scale was noticed in 27% and 3%. No significant differences between groups were observed concerning efficacy on histology ($P = 0.24$ at day 14; $P = 0.54$ at day 21), and for the physician global assessment ($P = 0.21$).

Adverse events, local tolerance

One or several adverse events were declared by 25% of patients in the mesalazine group vs. 16.9% in the hydrocortisone group (N.S.). The number and type of side-effects are shown on Table 3. Six patients (5%) in the mesalazine group stopped treatment for intolerance; the symptoms were anal or rectal burning in three cases, moderate abdominal pain in one case, headache and vomiting in one case and not detailed 'severe intolerance' in the last case. Three patients (3%) in the hydrocortisone group stopped treatment for intolerance; the symptoms were rectal bleeding in one case, abdominal pain in one case, anxiety and anal pruritis in one case. Acceptability of the treatment was judged by the patients who had reported an adverse event as good or fair in 63% and 67% in the mesalazine and hydrocortisone groups, respectively, (N.S.).

The percentage of patients reporting early rejection of the suppositories was 13% at day 1, 8% at day 3, and stabilized thereafter between 3 and 7%.

Table 3. Adverse events recorded on the diaries during treatment with mesalazine suppositories or hydrocortisone foam

	Mesalazine suppository (%)	Hydrocortisone foam (%)
Gastrointestinal disorders (bloating, gas, colic, diarrhoea)	9.8	10.2
Headache	1.5	—
Fatigue, weight loss, sleep disturbance	1.5	1.7
Miscellaneous: Back pain, skin rash*	5.3	16.9
Local discomfort	10.6	6.8

Differences = N.S.

DISCUSSION

This study was an open randomized multicentre trial comparing efficacy and tolerance of mesalazine microgranule suppositories (Pentasa) and hydrocortisone foam in 242 patients with active idiopathic proctitis. Mesalazine suppositories proved to be more efficient than hydrocortisone foam on the presence of blood in stools and mucus and on the degree of improvement of the endoscopy score. Both treatments were equally effective on the other symptoms (stool frequency and pain), and on the histological lesions, and both were well tolerated.

Statistical comparison of the characteristics of the patients randomly allocated to mesalazine or hydrocortisone showed no difference except for blood platelet counts which were slightly higher in the mesalazine group and the existence of previous episodes of proctitis which was higher in the mesalazine group. However, no difference was noticed for the existence of previous episodes of active proctitis in the year preceding inclusion. No indication exists in literature that these factors could have a relevant influence on the response to topical treatments.

Our results on the efficacy and tolerance of mesalazine and hydrocortisone are in accordance with literature.[1–12] A higher efficacy of mesalazine over steroid topical treatments has been observed in nine out of 10 comparative studies (including the present one).[1–6, 11, 12] The difference always concerned clinical symptoms, especially the disappearance of blood and mucus from stools. In the last comparative study, the absence of a significant difference between 3 g mesalazine and 30 mg prednisolone phosphate sodium enemas might be due to the long duration of the treatments (28 days) before assessment of their of the efficacy.[7] The precise mechanism for the better efficacy is unknown but it has been observed with different topical forms of mesalazine, i.e. enemas, foams and suppositories. Since steroids are potent anti-inflammatory drugs, one might hypothesize that other mechanisms of the healing process might also be triggered by mesalazine. Interestingly, recent data from Lémann *et al.*[6] suggested that the epithelial damage might be more responsive to local therapy with Pentasa than stromal inflammation. Our study confirms the data from Farup *et al.*[11] and shows that a single daily application of a controlled release 1 g suppository of mesalazine is more efficient than a rectal steroid foam in subjects with proctitis. A more pronounced effect on the healing of endoscopy lesions was also observed.

In our study, 25% of the patients in the mesalazine group and 17% in the hydrocortisone group (difference N.S.) reported adverse events. These included local side-effects (pain or anal irritation) in 11% of the subjects in the mesalazine group vs. 7% in the hydrocortisone group. General side-effects were more frequent than local side-effects, and consisted in half of the reports in digestive symptoms. Overall, side-effects led to the stopping of the drug in 5% and 3% of the patients on mesalazine and hydrocortisone, respectively. Although this result is slightly higher than in previous reports,[8–10, 13] it confirms the good acceptability of both treatments. The majority of the patients reporting adverse events reported that the overall acceptability of the treatment was good or fair.

It is commonly believed that subjects with proctitis would quickly reject suppositories, however, information on early rejections of topical treatments is scarce.[5, 13, 15] In our study, only 12% of the subjects had early rejection of the suppositories at the first administration, and this percentage rapidly fell to about 5%.

We conclude that mesalazine microgranule suppositories were as well tolerated as a hydrocortisone foam, and were more effective for some parameters of disease activity.

ACKNOWLEDGEMENTS

The authors thank the physician who took part in the study, and J. C. Charpentier for the statistical analysis.

This study was supported by a grant from Ferring S.A. France.

REFERENCES

1 Campieri M, Lanfranchi G, Bazzocchi G, *et al*. Treatment of ulcerative colitis with high-dose 5-aminosalicylic acid. Lancet 1981; ii: 270–1.

2 Danish 5-ASA Group. Topical 5-aminosalicylic acid vs. prednisolone in ulcerative proctosigmoiditis. A randomized, double-blind multicenter trial. Dig Dis Sci 1987; 32: 598–602.

3 Campieri M, Gionchetti P, Belluzzi A, *et al*. Efficacy of 5-aminosalicylic acid enemas vs. hydrocortisone enemas in ulcerative colitis. Dig Dis Sci 1987; 32 (December Suppl.): 67S–70S.

4 Lamers C, Meijer J, Engels L, *et al*. Comparative study of the topically acting glucocorticosteroid budesonide and 5-aminosalicylic acid enema therapy of proctitis and proctosigmoiditis. Gastroenterology 1991; 100: A223(Abstract).

5 Ngo Y, Rambaud JC. Lavement d'acide 5-aminosalicylique (Pentasa) vs. mousse d'acétate d'hydrocortisone (Proctocort) dans le traitement des poussées de rectite et rectosigmoïdite cryptogénétique. Gastroenterol Clin Biol 1992; 16: 558–63.

6 Lémann M, Galian A, Rutgeerts P, *et al*. Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. Aliment Pharmacol Ther 1995; 9: 357–62.

7 Mulder CJ, Tytgat GN, Wiltink EH, Houtoff HJ. Comparison of 5-aminosalicylic acid (3 g) and prednisolone phosphate sodium enemas (30 mg) in the treatment of distal ulcerative colitis. A prospective, randomized, double blind trial. Scand J Gastroenterol 1988; 23: 1005–8.

8 Campieri M, Gionchetti P, Belluzzi A, *et al*. 5-aminosalicylic acid as enemas or suppositories in distal ulcerative colitis? J Clin Gastroenterol 1988; 10: 406–9.

9 Ruddell WSJ, Dickinson RJ, Dixon MF, Axon ATR. Treatment of distal ulcerative colitis (proctosigmoiditis) in relapse: comparison of hydrocortisone enemas and rectal hydrocortisone foam. Gut 1980; 21: 885–9.

10 Sommerville KW, Langman MJS, Kane SP, MacGilchrist AJ, Watkinson G, Salmon P. Effect of treatment on symptoms and quality of life in patients with ulcerative colitis: comparative trial of hydrocortisone acetate foam and prednisolone 21-phosphate enemas. Br Med J 1985; 291: 866.

11 Farup PG, Hovde O, Halvorsen FA, Raknerud N, Brodin U. Mesalazine suppositories vs. hydrocortisone foam in patients with distal ulcerative colitis. Scand J Gastroenterol 1995; 30: 164–70.

12 Lee FI, Jewell DP, Mani V, *et al*. A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. Gut 1996; 38: 229–33.

13 Ngo Y, Gelinet JM, Ivanovic A, *et al*. Efficacité d'une application quotidienne d'un suppositoire de mésalazine (Pentasa) à libération progressive, dans le traitement des poussées de rectite ulcéro-hémorragique. Gastroenterol Clin Biol 1992; 16: 782–6.

14 Campieri M, Gionchetti P, Belluzzi A, *et al*. A controlled randomized trial comparing 5-aminosalicylic acid (5-ASA) 1 g once daily vs. 500 mg b.d. in treatment of active proctitis or distal proctosigmoiditis. Gastroenterology 1995; 108: A790 (Abstract).

15 Marteau P, Halphen, M. Etude comparative ouverte randomisée de l'efficacité et de la tolérance de lavements de 2 g d'acide 4-amino-salicylique (4-ASA) et de 1 g d'acide 5-amino-salicylique (5-ASA) dans les formes basses de rectocolite hémorragique. Gastroenterol Clin Biol 1995; 19: 31–5.