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Comparison of mesalazine suppositories in proctitis and distal proctosigmoiditis

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SUMMARY

Background: Mesalazine suppositories at 500 mg b.d. are a safe and effective treatment for patients with ulcerative proctitis or distal proctosigmoiditis. Recently a mesalazine 1 g suppository (Pentasa) has been developed.

Methods: Fifty patients with active ulcerative colitis extending not beyond 20 cm from the anus on sigmoidoscopy, participated in a randomized single-blind study comparing the efficacy, tolerance and acceptance of the new Pentasa mesalazine 1 g suppository, given once daily versus Claversal mesalazine 500 mg suppository b.d.

Results: After 2 weeks, clinical remission was observed in 16 of 25 (64%) in the Pentasa group and in 7 of 25 (28%) in the Claversal 500 mg b.d. treated group; sigmoidoscopic remission occurred in 13 of 25 (52%) in the Pentasa group and in six of 25 (24%) in the Claversal group ($P < 0.01$). After 4 weeks, clinical and sigmoidoscopic remission were observed, respectively, in 84 and 76% of patients treated with Pentasa suppositories, and in 80 and 72% of patients treated with Claversal suppositories 500 mg b.d. ($P =$ N.S.). The patients' evaluation for tolerability and practicality showed that the Pentasa suppository was significantly superior to the Claversal suppository.

Conclusions: Pentasa 1 g suppository once daily induces a quicker clinical and sigmoidoscopic remission, and was better tolerated, than the Claversal 500 mg suppository b.d., and it may represent an advance for the topical treatment of distal proctosigmoiditis.

INTRODUCTION

Topical treatment with mesalazine (5-aminosalicylic acid) has been shown to be effective for treatment of active distal ulcerative colitis when formulated either as enemas[1, 2] or suppositories.[3, 4]

While enemas reach the splenic flexure[5, 6] and are potentially suitable for patients with left-sided disease, suppositories, which have been shown to reach the sigmoid colon[7] represent a more practical and suitable approach than enemas in patients with proctitis or distal proctosigmoiditis.[8] A dose-ranging trial demonstrated that mesalazine suppositories 500 mg b.d., represent the optimal dose in active proctitis.[9]

Recently a new mesalazine 1 g suppository (Pentasa; Yamanouchi Pharma S.p.A., Milano, Italy) has been developed, from which the active ingredient, included in microgranules, is gradually released. This new suppository is small and has an oblong shape with a double apex, which facilitate its retention and retrograde spread.[10] This new suppository has been shown to be more effective than placebo,[11] and more effective than hydrocortisone acetate foam on rectal bleeding and presence of mucus in proctitis.[12]

The aim of this randomized, investigator-blind study was to compare the efficacy, tolerance and acceptance of the new mesalazine 1 g suppository once daily versus

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mesalazine 500 mg suppository (Claversal) b.d. in patients with active ulcerative proctitis or distal proctosigmoiditis.

MATERIALS AND METHODS

Selection of patients

The study was performed in accordance with the Declaration of Helsinki and all amendments, and was approved by the local Ethics Committee; all patients were informed of the nature and purpose of the study and gave their written consent.

Eligible patients were older than 18 years of age, with a diagnosis of active ulcerative proctitis or distal proctosigmoiditis (extending not beyond 20 cm from the anus) as confirmed by sigmoidoscopy and histology. Patients had to have a minimum score of 3 on a 12-point disease activity index (DAI) that measured stool frequency, rectal bleeding, endoscopic findings, and the physician's overall assessment of disease severity (Table 1).

Patients with previous history of unsuccessful treatment with topical mesalazine, and those treated with any rectally administered drug during the last 14 days were excluded. Patients with salicylate allergy or with concomitant active peptic ulcer or clinically important hepatic, renal, cardiovascular or psychiatric conditions were excluded. Pregnant or lactating women were excluded.

Immunosuppressive drugs were allowed until 3 months before entry to the study, and corticosteroid therapy until 2 weeks before the study. Oral sulphasalazine or mesalazine were allowed if the medication had been used regularly for more than 4 weeks before entry.

Table 1. Disease activity index and physicians' global assessment used in this study

Stool frequency	
0	Normal number of stools for this patient
1	1–2 stools more than normal
2	3–4 stools more than normal
3	≥5 stools more than normal
Rectal bleeding	
0	No blood found
1	Streaks of blood with stools less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passed
Sigmoidoscopic findings	
0	Normal or inactive disease
1	Mild disease (erythaema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythaema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment	
0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease

Study drugs

The study drugs consisted of suppositories containing 500 mg mesalazine (Claversal) and 1 g mesalazine (Pentasa).

Pentasa (mean weight 1569 mg) suppository contains mesalazine microgranules (not coated with ethylcellulose) compressed with Macrogol 6000, from which mesalazine is progressively released in the rectum (≈ 80% in 8 h). Figure 1 shows the size and shape of the Pentasa suppository compared with the Claversal suppository (mean weight 2100 mg); the Pentasa suppository is smaller (2.7 cm long vs. 3.2 cm) and has an oblong form with a double apex. Drugs were provided in blister packages and compliance was

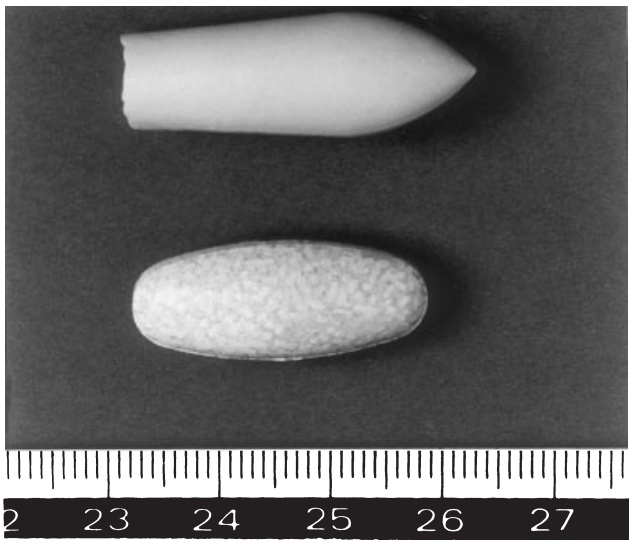

Figure 1. Claversal (upper) and Pentasa (lower) suppositories used

checked by the study personnel by counting returned unopened blisters and review of returned empty blister packs. Patients were considered non-compliant if they used less than 75% of the study drug during their treatment period or if they interrupted the study drug for more than 5 consecutive days.

Study design

The study was a 4-week randomized, single centre, investigator-blind study. Patients were randomly allocated to one of the two following treatments:

- Pentasa 1 g suppository once daily.
- Claversal 500 mg suppository twice daily.

Treatments were randomized according to a computer predetermined randomization list. Follow-up visits were planned after 2 and 4 weeks. Treatment was to continue throughout the 4 weeks of the study, unless the patients were withdrawn because of side-effects, were lost to follow-up, suffered an intercurrent illness or because of poor compliance (as defined above). Patients were free to withdraw from the study, if they wished, at any time.

Evaluation and scheduling

Symptoms assessment, medical histories, physical examination and endoscopic assessment were performed at baseline and after 2 and 4 weeks. Laboratory screening was performed at baseline and after 4 weeks, including haemoglobin, erythrocyte cell count, leucocyte cell count, platelet count, ESR, albumin, bilirubin, aspartate and alanine aminotransferases, alkaline phosphatase, creatinine and urine analysis. Stool culture to exclude infectious colitis was performed before study entry. Histological disease activity was also assessed at study entry and after 4 weeks according to Truelove & Richard criteria,[13] by a pathologist who was blinded to type of treatment, patient identification, time of assessment (entry vs. 4 weeks) and clinical status and was graded as follows: 0 = normal mucosa; 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.

Patients received diary cards to record their symptoms (stool frequency, bleeding, cramping, urgency) on a daily basis. They were also asked to record any other medications taken, other symptoms or possible side-effects and the number of hours that the suppository was retained.

Table 2. Scores of patients' opinions of formulations

Score	Practicality	Tolerability
3	No problems	Very good compliance
2	Minor problems (some trouble in inserting medication) or need to lie in bed	Good compliance but minor complaint (discomfort after administration)
1	Rather difficult, requiring assistance by another	Minimal compliance with major complaint (difficult to retain the medication, perianal irritation)
0	Not acceptable	Impossible to retain medication

Clinical assessments of therapy were made with the DAI and the physician's global assessment (PGA) scale, which ranges from 1 to 5. This scale is determined by the overall clinical assessment by the physician, based on patient symptoms, physical exam, laboratory data and endoscopic findings: 5 = much worse, 4 = worse, 3 = no change, 2 = minimally improved, 1 = much improved. PGA assessment was performed by a physician unaware of the type of treatment.

Clinical and endoscopic remission were defined as a score of zero in the clinical and sigmoidoscopic portion of DAI, respectively; histological remission was defined as a score of 1 in the histological activity disease index.

Patient's evaluation of therapy

At the end of the trial period (1 month) the patients were requested to express their opinion regarding practicality in self-administration and tolerability of the received formulation, according to a four-point score (Table 2).

Statistical analysis

In order to compare mean DAI score variations in each treatment group, between baseline, 2 weeks and 4 weeks, and to compare DAI scores at each interval between the two treatment groups, Student's *t*-test was used.

The proportion of PGA scores and of clinical, sigmoidoscopic (2 and 4 weeks) and histological (4 weeks) remission of treatment groups were compared using the

Table 3. Baseline characteristics of patients

	Pentasa	Claversal	*P*
Number of patients	25	25	n.s.
Mean age (range)	38 (24–46)	40 (26–48)	n.s.
Sex ratio (male/female)	15/10	13/12	n.s.
Duration of disease (years)	5.4	4.7	n.s.
Percent first episode	12	16	n.s.
Concurrent oral sulphasalazine or mesalazine	17	19	n.s.
Baseline overall disease activity index	6.50	6.23	n.s.
Previous use of topical mesalazine	21	22	n.s.

Table 4. Response to therapy

	Claversal		Pentasa	
Score	2 weeks	4 weeks	2 weeks	4 weeks
Much improved	9/25 (36%)	18/25 (72%)	*16/25 (64%)	20/25 (80%)
Minimally improved	8/25 (32%)	5/25 (20%)	3/25 (12%)	2/25 (8%)
No change	8/25 (32%)	2/25 (8%)	6/25 (24%)	3/25 (12%)
Worse	—	—	—	—
Much worse	—	—	—	—

* $P < 0.01$ vs. Claversal.

chi-squared test with Yates' correction. A two-tailed $P < 0.05$ was considered significant.

RESULTS

Fifty patients entered the trial: 25 were assigned to Pentasa 1 g suppository treatment, and 25 were assigned to Claversal 500 mg b.d. suppository. The two groups had similar demographic characteristics (Table 3). All patients completed the 4-week course of treatment. At baseline, individual patient DAI scores fell within the 3–12 range as required by the protocol, and mean total DAI scores for the two treatment groups were comparable.

Response to therapy

Response to therapy was assessed in three different ways. The physician's global assessment of the patient after 2 and 4 weeks (Table 4) showed that at 2 weeks the frequency of 'much improved' in the Pentasa group was significantly higher than in the Claversal group ($P < 0.01$), while the difference between treatments in PGA scores was not significant at 4 weeks.

Second, changes in the disease activity index were assessed. The mean disease activity index score (Table 5), decreased significantly in both treatment groups from baseline, both at 2 and at 4 weeks ($P < 0.001$); however at 2 weeks the decrease was significantly greater in patients receiving Pentasa compared with those treated with Claversal ($P < 0.001$).

Table 5. Summary of mean disease activity index (DAI) scores

	Observation		
Treatment group	Baseline	2 weeks	4 weeks
Claversal	6.23	3.47	1.14
Pentasa	6.50	*1.90	0.78

* $P < 0.001$ vs. Claversal.

Third the clinical, endoscopic (2 and 4 weeks) and histological (4 weeks) prevalence of remission were also analysed. After 2 weeks, clinical and sigmoidoscopic remission were observed in 16 of 25 (64%) and in 13 of 25 (52%) in the Pentasa group and in 7 of 25 (28%) and 6 of 25 (24%) in the Claversal group, respectively ($P < 0.01$). After 4 weeks, the percentage of patients in clinical, sigmoidoscopic and histological remission were not significantly different between the two groups of treatment (84%, 80% and 52% in the Pentasa group and 76%, 72% and 48% in the Claversal group, respectively).

Patient's evaluation of therapy

Patients questionnaire showed that patients treated with Pentasa scored 3 more frequently than patients in Claversal group in terms of tolerability ($n = 23$ vs. $n = 13$) ($P < 0.01$).

Moreover, no patients in the Pentasa group scored 1 or 0, while five patients in the Claversal group scored 1 for tolerability. The main problems reported by patients in the Claversal group were the difficulty in retaining the suppository administered in the morning and perianal irritation.

Side-effects

During the study no patients experienced side-effects, apart from the presence of perianal irritation reported in five patients treated with Claversal. No clinically significant changes from baseline values in haematology, blood chemistry or urine analysis were reported.

DISCUSSION

This study shows that treatment with this new mesalazine 1 g suppository once daily induces a quicker clinical and sigmoidoscopic improvement and remission compared with mesalazine 500 mg suppository b.d.

The results of the tolerability questionnaire confirmed the good acceptability of both forms of mesalazine suppository, although the single administration resulted in a more practical approach with a minor interference with the patients' daily activities.

The major recent advance in the treatment of ulcerative proctitis and proctosigmoiditis has been the advent of topical preparations of mesalazine, such as enemas and suppositories. Several controlled trials have proved the efficacy of mesalazine enemas in the treatment of active distal ulcerative colitis.[1, 2, 8, 13] The benefit of mesalazine suppositories in active proctitis or distal proctosigmoiditis have been shown in five placebo-controlled studies with 500 mg b.d. being the optimum dosage.[3, 4, 7, 9]

The preliminary results of the present open study suggest that the use of this new mesalazine microgranule 1 g suppository represents an efficient strategy for the topical treatment of ulcerative proctitis and distal proctosigmoiditis.

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