

Topical treatment with 5-aminosalicylic in distal ulcerative colitis by using a new suppository preparation

A double-blind placebo controlled trial

M. Campieri¹, P. Gionchetti¹, A. Belluzzi¹, C. Brignola¹, M. Tampieri¹, P. Iannone¹, G. Brunetti², M. Miglioli¹ and L. Barbara¹

¹ Institute of Clinical Medicine and Gastroenterology, University of Bologna, Italy

² Giuliani Medical Department, Milano, Italy

Accepted: 12 February 1990

Abstract. Sixty-two patients with ulcerative colitis localised to the distal sigmoid colon and rectum (<20 cm) entered the trial. Thirty-two were treated with 5-ASA 500 mg suppositories (Asacol) 3 times a day for 1 month while 30 received a placebo given in the same regime. Clinical, sigmoidoscopic and histological assessment was carried out before, after 15 days and after 1 month of treatment. At the end of the study 5-ASA suppositories showed significantly better results in all the parameters recorded than placebo ($p < 0.01$). There were no unwanted effects related to the use of suppositories. This treatment should therefore be offered as a first choice for patients with distal rectosigmoiditis.

Introduction

Topical treatment with 5-aminosalicylic acid (5-ASA) introduced per rectum has been shown to benefit patients with ulcerative colitis (UC) when formulated either as an enema or suppository [1–3].

While enemas seem to be a particularly suitable approach for patients with disease extending up to the splenic flexure because of its retrograde spread [4], suppositories have been shown to be the most acceptable preparation for patients with distal rectosigmoiditis [5]. Suppositories containing different dosages, ranging from 250 mg to 1 g, have been tried with good results [6]. With suppositories containing 250 mg a large number of suppositories may be necessary to treat the condition satisfactorily, while on the other hand the 1 g suppository often has a very good response but there may be incomplete dissolution in some patients.

The aim of our study was to compare the efficacy of a new suppository preparation containing 500 mg of 5-ASA, administered 3 times a day versus a placebo in a double-blind clinical trial.

Patients and methods

This study was approved by the Board of Senior Members of the Institution provided that a full explanation of the experimental design be given to all patients. Each patient fulfilling the medical criteria for entry was given such an explanation and asked to participate.

Sixty-two patients with mild to moderate attacks of ulcerative colitis agreed to take part in the study. Only patients with active inflammation limited to within 20 cm from the anal verge on sigmoidoscopy were included. A clinical, sigmoidoscopic and histological assessment was carried out at the beginning, after 15 days and one month, at which point the trial was terminated. Each assessment was carried out according to the criteria of Truelove and Richards [7] by physicians unaware of the administered topical treatment. According to these criteria only patients with mild or moderate attacks with fewer than 4–6 bowel actions daily were admitted. The number of motions passed by each patient daily with a semiquantitative determination of blood and mucus (from 1+ to 3+ + +) was recorded. Haematological assessment was conducted at the start of the study and after 1 month of treatment in order to exclude systemic effects. Endoscopic assessment was carried out using either a rigid or a flexible sigmoidoscope recording the presence or absence of hyperaemia, friability, contact bleeding and ulceration.

The histological assessment was carried out on a biopsy taken from the anterior rectal wall, generally at 10 cm from the anal verge. The grade of hyperaemia, mucus depletion, increase of inflammatory infiltration, and presence of crypt abscesses after 15 days and 1 month of treatment were compared with the pretreatment appearance.

Microbiological examination of stool was carried out to exclude infectious colitis.

For each assessment parameter, patients were judged as improved when there was a reduction of at least one grade from the baseline value according to the adopted evaluation scale. Patients were considered to be in clinical remission when there was a complete disappearance of symptoms; a sigmoidoscopic remission was considered when rectal mucosa was apparently repaired. Histological remission was considered when no sign of inflammation was seen in the biopsy.

Patients were randomly allocated to receive either three suppositories of 5-ASA daily or three placebo suppositories according to a predetermined random list. Characteristics of the patients are reported in Table 1. If any was taking oral sulphasalazine, this drug was maintained at the same dosage during the study. No rectal or systemic steroids were allowed during the study.

Table 1. Patient details

Age (years)	5-ASA (32 pts)	Placebo (30 pts)
Age (years)	37 ± 7	34 ± 8
Sex m/f	18/14	17/13
Extent of inflammation (cm)	14 ± 3	13 ± 2
Pts on maintenance treatment	10	12
Clinical activity		
Moderate	17	16
Mild	15	14
Sigmoidoscopic appearance		
Grade 3	3	2
Grade 2	15	16
Grade 1	14	12
Histological appearance		
Grade 3	4	4
Grade 2	16	15
Grade 1	12	11

Table 2. Outcome

	5-ASA (32 pts)		Placebo (30 pts)	
	15 days	30 days	15 days	30 days
Clinical				
No change	10	4	24	20
Improvement	14	10	5	8
Remission	8	18	1	2
Sigmoidoscopic				
No change	13	7	26	23
Improvement	14	12	3	5
Remission	5	13	1	2
Histological				
No change	16	11	27	26
Improvement	13	12	3	3
Remission	3	9	0	1

Each active suppository contained 500 mg of 5-ASA in solid semisynthetic glycerides with vegetable lecithin (Asacol).

5-ASA suppositories have been kindly provided by Giuliani Pharmaceutical Company with the trade name Asacol. Placebo suppositories have been supplied by the Hospital Pharmacy Department.

Clinical outcome

As can be seen from Table 2, there was a significant improvement in the 5-ASA treated group as compared with patients receiving a placebo preparation. After 15 days of treatment in the 5-ASA suppository group, 22 patients out of 32 were either in remission ($n=8$) or improved ($n=14$), while in the placebo group only 6 patients out of 30 were improved. At one month, 28 (87%) out of 32 5-ASA patients were either in clinical remission ($n=18$) or improved ($n=10$) compared with 10 out of 30 (33%) in the placebo group.

Sigmoidoscopic outcome

There was a significant difference in sigmoidoscopic appearance in the two groups, both after 15 days and at 1 month. After 15 days 19

(59%) out of 32 5-ASA patients either improved ($n=11$) or were in remission ($n=8$), and after 1 month 25 (78%) out of 32 were either in remission ($n=14$) or improved sigmoidoscopically ($n=11$). In contrast, only 11 (38%) out of 30 in the placebo group were in remission ($n=4$) or improved ($n=7$).

Histological assessment

There was a significant difference between the two groups of treatment. In the 5-ASA group 16 patients (50%) out of 32 were either in remission ($n=3$) or improved ($n=13$) at 15 days, while only 3 (10%) of patients did better in the placebo group. After one month in the 5-ASA group 21 patients (65%) out of 32 were either improved ($n=12$) or were in remission ($n=9$), while only 4 patients had an improved histological appearance in the placebo treated group.

Statistical analysis

Statistical analysis was performed using the chi-squared test. In all the assessment criteria evaluated, 5-ASA suppositories were significantly superior to placebo ($p < 0.01$).

Discussion

This study is a further demonstration of the efficacy of 5-ASA when given as suppositories for the management of patients with distal ulcerative colitis, and is in agreement with the findings preliminary obtained by Williams et al. who used 5-ASA 500 mg suppositories given 3 times daily [3].

One of the reasons for this positive outcome is certainly related to the retrograde spread of the products of dissolution of suppositories up to the rectosigmoid region as documented using ^{99m}Tc [3]. This is essential to allow optimal contact between 5-ASA and the inflamed mucosa [8].

All patients showed excellent compliance with 5-ASA suppository treatment and claimed that this was an extremely easy therapeutic approach with no difficulty or discomfort. These findings confirm previous evidence that suppositories should be the first choice treatment for patients with distal sigmoiditis, particularly because of its ease of administration and convenience to the patient [5]. No side-effects were observed and this can probably be related to the negligible absorption of 5-ASA when given as suppositories, and of course, to the absence of sulphapyridine from the formulation [9]. Having obtained such good and prompt improvement of symptoms in these patients, there is now the need to find out whether these beneficial results can also be obtained by reducing the number of daily suppositories. Further study should aim to find out the minimum dosage necessary to give the maximum benefit.

References

1. Campieri M, Lanfranchi GA, Bazzocchi G, Brignola C, Sarti F, Franzin G, Battocchia A, Labo G, Dal Monte PR (1981) Treatment of ulcerative colitis with high-dose 5-aminosalicylic acid enemas. *Lancet* 2: 270-271

2. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, Martin T, Sparr L, Prokipchuk E, Lowell B (1987) 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis and proctitis. *Gastroenterology* 92:1894-1898
3. Williams CN, Haber G, Aquino JA (1987) Double-blind, placebo controlled evaluation of mesalazine suppositories in active distal proctitis and measurements of extent of spread using ^{99m}Tc-labeled mesalazine suppositories. *Dig Dis Sci* 32:71s-75s
4. Campieri M, Lanfranchi GA, Brignola C, Bazzocchi G, Gionchetti P, Minguzzi MR, Cappello IP, Corbelli C, Boschi S (1986) Retrograde spread of 5-aminosalicylic acid enemas in patients with active colitis. *Dis Colon Rectum* 29:108-110
5. Campieri M, Gionchetti P, Belluzzi A, Brignola C, Tabanelli GM, Miglioli M, Barbara L (1988) 5-aminosalicylic acid as enemas or suppositories in distal ulcerative colitis? *J Clin Gastroenterol* 10:406-409
6. Campieri M, Gionchetti P, Belluzzi A, Brignola C, Torresan F, Tampieri M, Iannone P, Miglioli M, Barbara L (1989) 5-aminosalicylic acid suppositories in the management of ulcerative colitis. *Dis Colon Rectum* 32:398
7. Truelove SC, Richard WCD (1956) Biopsy studies in ulcerative colitis. *Br Med J* 1:1315-1318
8. Nielsen OH, Bukhave K, Elmgreen J, Ahnfelt-Ronne (1987) Inhibition of 5-lipoxygenase pathway of arachidonic acid metabolism in human neutrophils by sulphasalazine and 5-aminosalicylic acid. *Dig Dis Sci* 32:577-582
9. Klotz U (1985) Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid. *Clinical Pharmacokinet* 10:285-302

Dr. M. Campieri
Istituto di Clinica Medica
e Gastroenterologia
Policlinico S. Orsola
Via Massarenti 9
I-40138 Bologna
Italy