

Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study

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Abstract

Background—Daily administration of rectal formulations of mesalazine is effective in preventing relapse of ulcerative proctitis. Maintenance of remission with lower doses would be an advantage.

Aim—The efficacy of mesalazine suppositories (Pentasa) 1 g three times a week *v* placebo to maintain remission in patients with cryptogenetic proctitis was studied.

Methods—Ninety five patients with cryptogenetic proctitis were randomised within two weeks of remission to receive for one year or until relapse three suppositories per week of either Pentasa (n=48) or placebo (n=47). In the case of a relapse, the patients received one suppository/day.

Results—It was found that 25 of 48 subjects *v* 18 of 47 remained in remission in the mesalazine and placebo groups respectively. The relapse rate was lower in the mesalazine group for the following time intervals: 0–90 days (19% *v* 38%, $p=0.035$), 0–180 days (29% *v* 54%, $p=0.017$), 0–270 days (38% *v* 60%, $p=0.031$), and 0–365 days (48% *v* 62%, $p=0.18$). Treatment of relapse with one suppository/day induced remission in 11 of 18 and 2 of 26 patients in the mesalazine and placebo groups respectively ($p=0.001$). Overall, 61% *v* 28% patients remained in the protocol and were in remission at one year ($p=0.001$). Tolerance was good.

Conclusion—Mesalazine suppositories 1 g three times a week are effective for preventing relapses of cryptogenetic proctitis. Increasing the dose to 1 g/day is effective in a high proportion of subjects who relapsed.

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Keywords: inflammatory bowel disease; mesalazine; 5-aminosalicylic acid; topical treatments; proctitis

The efficacy of oral 5-aminosalicylic acid (5-ASA) in treating acute episodes of ulcerative colitis and in preventing relapse is well established.¹ Topical treatments for distal disease with mesalazine enemas, rectal foams, or suppositories are also effective and well tolerated in treating acute episodes, and appear to have a quicker effect in relieving symptoms than oral treatments.² Mesalazine enemas have been shown to be effective in preventing relapse in several studies using 20–30 g 5-ASA

per month.^{3–9} Two studies have been performed with suppositories.^{10, 11} In the first, a daily administration of a 500 mg 5-ASA suppository—that is, 30 suppositories, 15 g 5-ASA/month—maintained remission in 61% of the patients at one year and 45% at two years.¹⁰ In the second, twice daily administration of 400 mg suppositories—that is, 60 suppositories, 24 g 5-ASA/month—maintained remission in 12 of 15 subjects compared with three of 15 in the placebo group.¹¹ The two studies used glycerine suppositories, and none used slow release mesalazine suppositories. Slow release mesalazine suppositories differ from classical suppositories in three ways: (a) they consist of microgranules while classical suppositories use glycerine for an excipient; (b) microgranules allow a slower release of the 5-ASA than glycerine; (c) they contain 1 g 5-ASA while the other suppositories contain only 400–500 mg. Mesalazine slow release suppositories have been found to induce remission of distal ulcerative colitis more rapidly and efficiently than classical suppositories.¹² The present randomised double blind placebo controlled trial aimed to assess the efficacy of slow release mesalazine suppositories (Pentasa), 1 g administered three times per week—that is, 13 suppositories, 13.3 g/month (low maintenance dose) *v* placebo, in preventing relapse of ulcerative proctitis as well as to compare the efficacy of 1 g/day *v* placebo in patients who relapsed with the low maintenance dose. This protocol thus used a lower 5-ASA cumulative dose than the previous studies in the literature and fewer rectal administrations.

Patients and methods

The study protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Médicale. Each patient gave written informed consent before entry into the trial. Patients were recruited from 22 centres in France, all in the Northern part and the Paris area, except for two in Toulouse.

Subjects with cryptogenetic proctitis were eligible for the study if they were older than 18, were not pregnant, had lesions limited to the rectum, had experienced at least two episodes of acute proctitis in the year preceding inclusion, and were in clinical remission for less than two weeks at inclusion with an endoscopy score of 0 or 1. Clinical remission was defined as no rectal bleeding, no mucus in the stools, no diarrhoea, no pain, and no tenesmus.

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Endoscopy lesions were scored for severity as follows: 0, normal mucosa or erythema; 1, granularity or oedema or lack of the normal vascular pattern; 2, contact bleeding; 3, spontaneous bleeding; 4, superficial ulcerations; 5, deep ulcers.¹³ Exclusion criteria were as follows: cause of proctitis other than ulcerative colitis (infectious, drug induced, radiotherapy, Crohn's disease), pregnancy, hypersensitivity to salicylates, resistance to salicylates during a previous acute episode, any other maintenance treatment of ulcerative colitis except previously prescribed oral salicylates provided that the dose was not changed during the whole study period.

STUDY DESIGN

The study was randomised, double blind, and placebo controlled. Randomisation was performed within each centre using sealed envelopes. Subjects were assigned to be administered a low maintenance dose, which consisted of three times per week (and not on two consecutive days) either placebo suppositories or 1 g mesalazine suppositories (Pentasa, Ferring, Gentilly, France) for 12 months or until relapse.

Follow up was carried out by the same doctor at one, three, six, nine, and twelve months, and in the case of relapse. The following parameters were recorded: number of bowel movements per day, presence of blood discharge or mucus in stools, presence and intensity of tenesmus and abdominal pain, and any adverse event. Consultations at three and nine months could be replaced by a phone interview. A rectoscopy was performed at least at one, six, and twelve months, and in the case of relapse. The primary outcome measure was the time until relapse. Relapse was defined as the occurrence of clinical symptoms with an increase in the endoscopy score ≥ 1 when compared with the endoscopy score at entry, or occurrence of rectal bleeding more than twice in one day. Secondary endpoints were the number of patients with relapse, the characteristics of the relapse, and the efficacy of the one suppository/day dose to induce remission in the patients who experienced a relapse.

In the case of a relapse, the dose was increased to one suppository/day. If remission was obtained, this dose was maintained until the end of the one year trial. If remission was not obtained after 15 days, the doctor and

patient were allowed either to continue the treatment for another 15 days or to stop the trial and consider the result as a treatment failure. If remission was not obtained during the 30 days after relapse, treatment was considered as a failure.

SAMPLE SIZE DETERMINATION AND STATISTICAL METHODS

From previous studies on the effect of topical salicylates on the relapse rate of distal ulcerative colitis, we estimated that placebo and mesalazine could have an efficacy of 35 and 70% respectively. The number of subjects required to be studied to detect this decrease in relapse rate with a log rank test, a type I error of 0.05, and a power of 90% is 93.¹⁴

Results are expressed as means (SD) or 95% confidence intervals (CI). The main analysis was on an intention to treat basis and included all randomised patients. Student's *t* test and the Wilcoxon test were used to compare quantitative variables. The χ^2 test was used to compare qualitative variables. Relapse free actuarial curves were established. Time to relapse curves were estimated using the Kaplan-Meier technique.¹⁵ The difference between curves was compared with a two sided log rank test. The number of patients relapsing during the study were compared using the Mantel-Haenszel test adjusted on the number of episodes of relapse in the preceding year. Comparison of the risk of relapse within time intervals was made using the χ^2 test.

Results

Ninety five patients were included (48 in the mesalazine group, 47 in the placebo group) from March 1993 to October 1994—that is, until the required number of patients had been reached. During the same period of time, eight patients who fulfilled the inclusion criteria refused to participate in the study as it was placebo controlled, and were therefore not included. The two groups did not differ with respect to age, sex, number of proctitis episodes in the preceding year, symptoms and endoscopy scores, extent of proctitis, or associated oral treatment (table 1). The duration of the episode preceding inclusion was significantly longer in the mesalazine group (table 1). Twenty seven subjects in the mesalazine group and twenty four in the placebo group had been receiving oral maintenance treatment since before the relapse of proctitis and this was maintained throughout the study. This oral treatment consisted of 5-ASA in 24 and 23 subjects of the mesalazine and placebo groups respectively with a daily dose of 1.9 (0.8) g in each group, and sulphasalazine (three *v* one subjects). Fifty five patients (19 and 36 in the mesalazine and placebo groups respectively, $p=0.001$) stopped the protocol because of failure or dropped out. The reasons for drop out were: lost to follow up (two and one in the mesalazine and placebo groups respectively), pregnancy (two cases in each group), intolerance (one and two), decision of the patient (four and seven). Figure 1 shows the numbers of patients studied at each step of the protocol.

Table 1 Patient characteristics at entry (where applicable, results are expressed as means (SD))

	Mesalazine	Placebo	<i>p</i> Value
Number of patients	48	47	
Percentage men	52.1	40.4	0.26
Age (years)	41.5 (13.5)	41.2 (11.8)	0.89
No of episodes in the last year	2.6 (1.5)	3.1 (2.1)	0.35
Duration of the last episode (days)	77 (68)	57 (63)	0.039
Oral treatment (% subjects)	56.3	53.2	0.77
No of stools/day	1.8 (1.6)	1.6 (1.0)	0.97
Blood in stools (% subjects)	0	0	
Mucus (% subjects)	10.4	4.3	0.44
Tenesmus (% subjects)	16.7	10.6	0.43
Pain (% subjects)	25.0	21.2	0.65
Endoscopy score 0 (% subjects*)	50.0	44.7	0.60
Extent of lesions (cm)	9.6 (6.8)	7.6 (6.0)	0.18

*Score = 1 in the others.

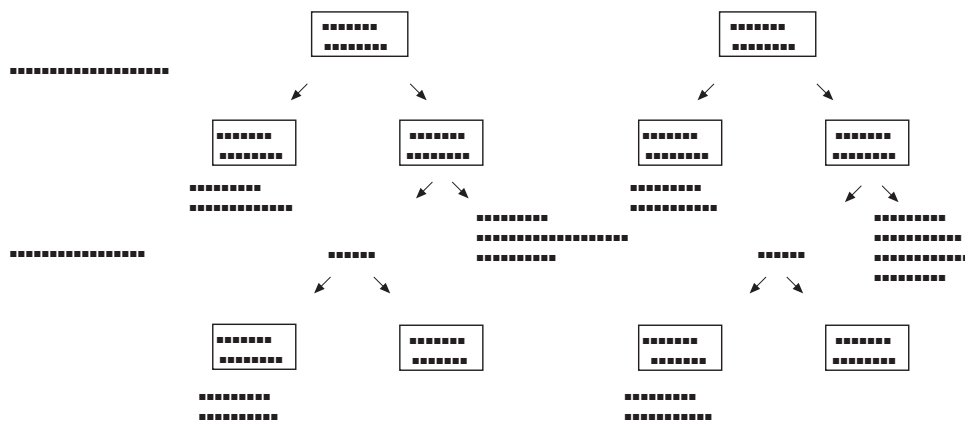


Figure 1 Flow chart of the numbers of patients studied at the different steps of the protocol comparing the efficacy of mesalazine and placebo suppositories to maintain remission of ulcerative proctitis over one year.

EFFICACY OF THE LOW MAINTENANCE DOSE

Figure 2 shows the survival curves without relapse in both groups with the three suppositories/week dose. The mean survival without relapse was 239 days (CI 203 to 275) v 166 days (CI 130 to 201) in the mesalazine and placebo groups respectively (log rank test: $p=0.067$). Table 2 gives the reduction of the risk of relapse depending on time intervals. The risk of relapse was not significantly influenced in any group by the endoscopy score at entry (0 or 1) (log rank $p=0.26$). It was also not influenced by the presence or absence of associated oral treatment ($p=0.25$). In the mesalazine group, the mean time until relapse was 227 days (CI 175 to 279) compared with 230 days (CI 188 to 273) for the subjects with and without associated oral treatment respectively. In the placebo group, the mean time until relapse was 136 days (CI 100 to 172) v 175 days (CI 120 to 229) for the subjects with and without associated oral treatment respectively.

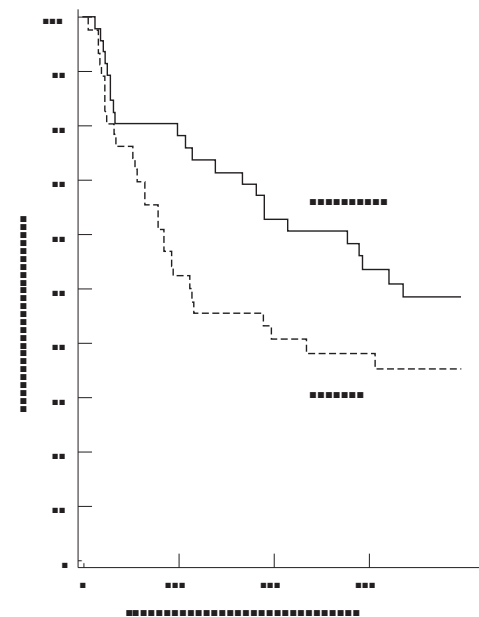


Figure 2 Time to relapse. Relapse was defined as occurrence of clinical symptoms with an increase in the endoscopy score ≥ 1 when compared with the endoscopy score at entry, or occurrence of rectal bleeding more than twice in one day.

CHARACTERISTICS AND TREATMENT OF RELAPSE

The clinical symptoms and endoscopic lesions observed in the patients who relapsed did not differ significantly between the two groups except for the presence of tenesmus which was less frequently observed in patients in the mesalazine group (table 3). When the dose regimen was increased to one suppository/day, remission was obtained in 61% v 8% of the patients in the mesalazine and placebo groups respectively ($p=0.001$). Overall, 61% v 28% of the patients of the mesalazine and placebo groups respectively remained in the protocol and were in remission at one year ($p=0.001$).

ADVERSE EVENTS AND LOCAL TOLERANCE

One or several adverse events were reported by six of the patients in the mesalazine group and five in the placebo group ($p=0.72$). They consisted of: anal or rectal pain or difficulty with introducing the suppository in four cases in each group; one case of asthenia, hypotension, and moderate leucopenia at nine months of treatment (mesalazine), which resolved without changing the treatment; one case of mild hair loss after one month of treatment (mesalazine), which was found not to be significant by the patient and doctor (treatment was followed for one year). One patient in the mesalazine group and two in the placebo group stopped treatment because of intolerance; the symptoms were anal or rectal burning in all three cases.

Discussion

This study shows that one mesalazine slow release suppository (Pentasa, 1 g) administered three times a week is effective in preventing or delaying recurrence of ulcerative proctitis, and that remission can be induced by increasing the dose to one suppository a day in 61% of the patients who relapse with the low dose.

Efficacy of oral mesalazine in treating acute episodes and preventing relapses of ulcerative colitis is well established.¹ Topical treatments with mesalazine have a quicker effect in distal forms of the disease.² Daily administration of 5-ASA enemas or suppositories is effective in preventing relapse of ulcerative proctitis or proctosigmoiditis.^{3 7 8 10 11} Several authors sub-

Table 2 Risk of relapse of distal ulcerative colitis in the patients receiving three suppositories a week of either 1 g mesalazine or placebo

Time interval (days)	Mesalazine No (%)	Placebo No (%)	p Value
0-90	9/45 (19)	18/46 (38)	0.035
0-180	13/45 (29)	25/46 (54)	0.017
0-270	17/45 (38)	28/46 (60)	0.031
0-365	22/45 (48)	29/46 (62)	0.18

Table 3 Characteristics of relapse of distal ulcerative colitis in the patients receiving three suppositories a week of either 1 g mesalazine or placebo (where applicable, results are expressed as means (SD))

	Mesalazine	Placebo	p Value
Number of patients	23	29	
No of stools/day	3.2 (1.8)	3.4 (2.0)	0.91
Blood in stools (% subjects)	91.3	100	0.26
Mucus (% subjects)	43.5	64.3	0.14
Tenemus (% subjects)	39.1	65.5	0.024
Pain (% subjects)	43.5	51.7	0.39
Extent of lesions (cm)	9.4 (5.6)	11.4 (6.9)	0.58
Endoscopy (% subjects)			0.54
Score 1	9.5	4.2	
Score 2	47.6	41.7	
Score 3	28.6	41.7	
Score 4	14.3	12.4	

sequently proposed new schedules to decrease the cumulative 5-ASA dose and the numbers of administrations. Miner *et al*⁷ reported that one 1 g enema every other day was more effective than placebo but that one administration every three days was not. The same trend was reported in an uncontrolled trial.⁹ Three protocols were described which proved to maintain remission in about 75% of subjects at one year; they consisted of two 4 g enemas/week,⁴ one 4 g enema/day for the first seven days of each month,⁵ and one 4 g enema every three days.⁶ Thus the doses of 5-ASA tested up until now were always greater than 20 g/month except in the study of Hanauer *et al*¹⁰ who administered suppositories daily. The advantages of the treatment that we chose in the present protocol over the previous protocols are the lower cumulative doses of 5-ASA used and the fewer suppository administrations. Furthermore suppositories are often considered by patients as more acceptable.

Half of the subjects studied were also receiving oral treatment with aminosaliclates, and it might be argued that this treatment which is often effective might participate in the therapeutic effect. However, the results were similar in the subjects who received only suppositories. The subjects who received both oral and local treatment had been included when they had experienced a relapse of proctitis despite the oral treatment; these selected patients were thus resistant to the prophylactic oral treatment, and our results suggest therefore that local treatment could be more efficient than the oral treatment at a dose of 2 g/day in maintaining remission.

In the present study, the efficacy of the low maintenance dose was significant up to nine months but not after one year (48% relapses *v* 62%). It may thus be reasonable to try to stop topical maintenance treatment after a few months, and to prescribe a more prolonged

treatment at the lowest effective dose only in patients who relapse. About 61% of the subjects who relapsed despite receiving three suppositories of Pentasa per week responded to the dose increase and underwent remission with one suppository a day. There is therefore no indication that chronic administration of low doses may decrease the responsiveness to the higher doses needed to treat a relapse. Eight subjects who had relapsed when on the lower maintenance dose dropped out, and were not included in the second part of the study. If all these subjects of the mesalazine group had relapsed with one suppository/day and all of those in the placebo group had remained in remission, the difference in efficacy would still be in favour of the 5-ASA maintenance treatment (48% *v* 17%, *p*<0.02). The overall strategy to begin maintenance treatment with the low dose in every subject and to increase this dose to one suppository a day in the case of a relapse is more economical than daily administration from the beginning; it proved effective in 61% of the patients. Interestingly, the efficacy was no different whether the three times per week maintenance treatment was started in subjects with endoscopy scores of 0 or 1. This suggests that the decision to decrease the dose from 1 g daily, which is used to treat acute episodes, to the maintenance dose can be taken even in patients with endoscopy lesion scores of 1. This study confirms that the tolerance to Pentasa suppositories is good; only one subject out of 47 had to stop the long term treatment because of intolerance. It also confirms that using a long term topical treatment did not imply an increased frequency of relapse with disease extension.⁵

We conclude that treatment with one 1 g Pentasa slow release suppository three times a week is an effective and safe treatment for preventing or delaying relapses of ulcerative proctitis in subjects with high risk of relapse. Increasing the dose to one 1 g mesalazine suppository a day is efficacious in two thirds of patients who relapse while receiving this low dose.

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