

Clinical trials

Comparison of delayed release 5-aminosalicylic acid (mesalazine) and sulphasalazine in the treatment of mild to moderate ulcerative colitis relapse

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SUMMARY Oral formulations of 5-aminosalicylic acid (mesalazine) appear less toxic than sulphasalazine. We have therefore compared sulphasalazine, low dose mesalazine and high dose mesalazine in the treatment of mild to moderate relapse of ulcerative colitis. Sixty one patients (32 men, aged 20-78 years) were randomly allocated to sulphasalazine 2 g daily, mesalazine 800 mg daily, or mesalazine 2.4 g daily in a double blind, double dummy, four week trial. Groups were comparable for age, sex, extent of disease, and pretrial sulphasalazine intake. Four patients were unable to complete the study because of treatment failure (two taking sulphasalazine and two high dose mesalazine). A further two patients taking sulphasalazine developed side effects necessitating withdrawal. Within treatment comparisons revealed significant improvement of: sigmoidoscopic grade in the sulphasalazine group; rectal bleeding, sigmoidoscopic and histological grade in the low dose mesalazine group; stool frequency, rectal bleeding and sigmoidoscopic grade in the high dose mesalazine group. Greater improvement in rectal bleeding ($p < 0.05$) and sigmoidoscopic appearances ($p < 0.05$) occurred in patients taking high dose mesalazine than in those taking sulphasalazine. In two patients taking high dose mesalazine minor rises of plasma creatinine concentrations occurred, suggesting the need to monitor renal function.

Although the main value of sulphasalazine (SSZ) is in the maintenance of ulcerative colitis remission¹⁻³ it is also of benefit in active disease.^{4,6} Many patients, however, are unable to take the drug as side effects are common, particularly at high doses.⁷ As most of these side effects are similar to those seen with sulphonamide drugs and as they correlate well with plasma sulphapyridine concentrations it seems likely that the sulphapyridine component of SSZ is responsible for much of the drug's toxicity.⁸ Therapeutic activity, on the other hand, seems to reside in the 5-aminosalicylic acid (5-ASA) component of SSZ.⁹⁻¹⁴

Unfortunately, 5-ASA is unstable in gastric acid and is rapidly absorbed from the small intestine.¹⁵ As

its mode of action is thought to be predominantly topical¹⁶ oral formulations have been developed to deliver 5-ASA to its site of action.

We have studied a delayed release form of 5-ASA (mesalazine) which relies on its coating, Eudragit S, to release 5-ASA in the colon. Coat dissolution is pH-dependent occurring rapidly above pH 7, the prevailing pH of the distal small intestine and colon.¹⁷⁻¹⁹ The aim of the present study was to compare sulphasalazine, equivalent dose mesalazine and high dose mesalazine in the treatment of mild to moderate ulcerative colitis relapse.

Methods

PATIENT SELECTION

Patients were recruited from three hospitals in close geographical proximity. The study population com-

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prised adult outpatients with mild to moderate ulcerative colitis relapse. Patients with relapse of established colitis, and those presenting as a first attack were included. All were passing blood at least once per day and all had a haemorrhagic rectal mucosa. Patients with systemic upset, usually indicating a need for treatment with corticosteroids, were excluded. No patient had received either oral or rectal steroids within two weeks of trial entry. Those taking other drugs known to have an effect on colitis activity, patients with significant hepatic or renal disease and those with a history of salicylate allergy were excluded. All patients had a negative stool culture on trial entry. The study protocol was approved by the three independent hospital ethical committees and patients gave written informed consent before study.

STUDY DESIGN

The study followed a randomised, double blind protocol. All medications were prepackaged in order to ensure an equal and random distribution to each centre. Patients were assigned to one of three treatment limbs: (a) enteric-coated SSZ 1 g twice daily (Salazopyrin EN, Pharmacia); (b) an equivalent dose of delayed release mesalazine, 400 mg twice daily (Asacol, Tillotts Laboratories); or (c) a three fold larger dose of delayed release mesalazine, 1200 mg twice daily. As the tablets differ in shape, size, colour and dose of 5-ASA per tablet a double dummy technique was used, each patient receiving three sets of medication, two placebo and one active.

Throughout the study all clinical assessments were undertaken by one investigator. On entry to the trial a complete history and physical examination including rigid sigmoidoscopy were carried out. The macroscopic appearances of the rectal mucosa were graded on a predetermined scale (Table 1). The severity of the mucosal changes were recorded at three sites within the rectum: in the lowest 5 cm, between 5 and 10 cm, and above 10 cm with reference to the anal margin. A rectal biopsy was taken from the anterior rectal wall between 5 and 10 cm.

Haematological (full blood count, sedimentation rate, serum and red cell folate concentrations) and biochemical variables (multichannel analysis) were measured on entry and urine samples were tested for blood and protein using a semiquantitative dip stick (Multistix, Ames).

Each patient kept a daily symptom diary in which they recorded stool frequency, bleeding, mucus, abdominal pain, possible side effects, and other symptoms they felt relevant. Patients attended for follow up at two and four weeks or at any other time should they wish. At each attendance bowel habit was recorded and corroborated with the symptom

Table 1 *Sigmoidoscopic and histological grading systems*

<i>Sigmoidoscopic grading</i>		<i>Histological grading</i>	
<i>Grade</i>	<i>Macroscopic appearance</i>	<i>Grade</i>	<i>Microscopic appearance</i>
0	Normal, vascular pattern clearly visible	0	Normal
1	Erythema with loss of vascular pattern	1	Mild increase in chronic inflammatory cell infiltrate, no tissue destruction
2	As above plus contact bleeding	2	Moderate increase in chronic inflammatory cell infiltrate, no tissue destruction
3	As above plus spontaneous bleeding	3	Marked increase in chronic inflammatory cell infiltrate, mild tissue destruction
4	As above plus obvious ulceration	4	Marked increase in chronic inflammatory cell infiltrate, obvious tissue destruction

diary. General well being was graded and patients were questioned as to the occurrence and frequency of a list of 15 possible side effects. Vital signs were recorded and abdominal examination done. A urine specimen was tested at each clinic visit and blood tests were repeated on completion of the study. Unused tablets were returned to assess drug compliance.

Patients were followed to either withdrawal or completion at four weeks at which time a further sigmoidoscopy and biopsy were done. Trial medications were then discontinued and oral SSZ and, if necessary, corticosteroid treatment prescribed.

On completion of the study histological analysis of the biopsy specimens was undertaken. Five micron thick paraffin embedded sections were stained with haematoxylin and eosin, coded and each examined independently by two histopathologists who had no knowledge of either the patients or treatments given. The histological changes were graded on a predetermined scale (Table 1), the final grade being the mean of the two assessments.

STATISTICAL ANALYSIS

Results are expressed as median and range unless otherwise stated. Within treatment comparisons were made using Wilcoxon's matched pairs test whereas between treatment comparisons were made using the χ^2 or Fisher's exact test. A 5% two tailed significance level was used in each case.

Results

PATIENTS

Sixty one patients entered the study, 32 men and 29

women, ages ranged from 20–78 years. One patient defaulted leaving 19 in the SSZ group, 20 in the low dose mesalazine group and 21 patients in the high dose mesalazine group.

Patient and disease characteristics are shown in Table 2. The three groups were comparable with respect to age, sex, presentation as either relapse or first attack and pretrial SSZ intake. Disease extent as judged by either double contrast barium enema or the macroscopic appearances of the mucosa at colonoscopy was also similar. Disease duration was the only variable not matched as patients randomised to low dose mesalazine had a significantly longer duration of disease.

RESPONSE TO TREATMENT

On entry to the study the three groups were matched for stool frequency, rectal bleeding, sigmoidoscopic, and histological grade. Within treatment comparisons revealed significant improvement of: sigmoidoscopic grading above 5 cm in the SSZ group; rectal bleeding and all sigmoidoscopic grades in the low dose mesalazine group and stool frequency, rectal bleeding and all sigmoidoscopic grades in the high dose mesalazine group (Table 3). Significant improvement in histological grade occurred only in the low dose mesalazine group although significance in the high dose group approached the 5% level. Four patients, two allocated SSZ and two high dose mesalazine, suffered significant clinical deterioration and were unable to complete the four week study period.

Between treatment differences were only statistically significant when comparing the high dose mesalazine and SSZ group. On trial entry 95% of patients allocated SSZ, 85% allocated low dose

Table 2 Patient and disease characteristics

	SSZ n=19	ASA(L) n=20	ASA(H) n=21
Age (years)	45 (20–78)	34 (24–64)	34 (23–76)
Sex ratio	11M:8F	9M:11F	12M:9F
Presentation			
First attack	8	9	9
Relapse	11	11	12
Duration (weeks)			
First attack	12 (6–36)	40 (3–156)	12 (6–52)
Relapse	4 (2–12)	8 (3–104)	6 (3–156)
Disease extent			
Total	1	1	1
Left sided	3	2	5
Proctosigmoiditis	8	9	8
Proctitis	7	8	7
Pretrial SSZ maintenance	7	7	8

ASA(L) – low dose mesalazine, 400 mg twice daily; ASA(H) – high dose mesalazine, 1200 mg twice daily; median (range).

Table 3 Response to treatment

	SSZ	ASA(L)	ASA(H)
Stool frequency/day			
Entry	4 (2–8)	3.5 (1–8)	5 (1–10)
Completion	3 (1–7)	2.5 (1–7)	2 (1–7)†
Rectal bleeding/day			
Entry	3 (1–8)	3 (1–7)	3 (1–8)
Completion	3 (0–5)	1 (0–6)*	1 (0–7)†
Sigmoidoscopic grade			
0–5 cm Entry	3 (2–3)	3 (2–4)	3 (2–3)
Completion	2 (1–4)	2 (1–4)†	2 (1–4)*
5–10 cm Entry	3 (2–4)	3 (1–4)	3 (2–3)
Completion	2 (1–4)*	1 (0–4)†	2 (0–4)*
>10 cm Entry	3 (2–4)	3 (1–4)	2 (2–3)
Completion	2 (1–4)*	1.5 (0–4)†	1 (0–4)*
Histological grade			
Entry	3 (2–4)	3 (1–4)	3 (2–4)
Completion	3 (1.5–4)	2 (0–3)*	2.5 (1–4)

Median (range); within treatment significance: * $p < 0.005$; † $p < 0.01$.

mesalazine and 95% allocated high dose mesalazine were passing three or more stools per day. On completion of the study the percentages had fallen to 47%, 30%, and 19% respectively ($p < 0.1$ high dose mesalazine *versus* SSZ).

All patients were passing blood at least once daily on entry to the study. Improvement in rectal bleeding occurred in 47% taking SSZ, 75% taking low dose, and 81% taking high dose mesalazine ($p < 0.05$ high dose mesalazine *versus* SSZ). Symptomatic remission (resolution of rectal bleeding and three or less stools per day) was seen in 21%, 30%, and 43% of the groups respectively ($p < 0.2$).

All patients included in the study had sigmoidoscopic evidence of active disease (grade 2 or more, Table 1). After four weeks' treatment significant improvement (grade 1 or less) was seen in 5% of patients receiving SSZ, 25% receiving low dose and 33% high dose mesalazine ($p < 0.05$ high dose mesalazine *versus* SSZ). No significance between treatment differences was apparent with respect to histological grade.

Pretrial SSZ intake appeared to be a major predictor of treatment outcome. Of the 23 patients taking SSZ at trial entry, only 13 patients improved and only two achieved symptomatic remission during the four week trial. In the group of 37 patients not taking SSZ at trial entry, however, 31 patients improved and 17 achieved symptomatic remission ($p < 0.005$). The influence of pretrial SSZ intake on treatment outcome by treatment group is shown in Table 4.

SIDE EFFECTS AND LABORATORY VALUES

Two patients were unable to complete the study because of drug related side effects. One patient

Table 4 The influence of pretrial SSZ intake on treatment outcome

	SSZ		ASA(L)		ASA(H)	
	+	-	+	-	+	-
Pretrial SSZ intake	+	-	+	-	+	-
Patients/group	7	12	7	13	9	12
Number improved (%)	1(14)	9(75)	5(71)	11(84)	7(77)	11(92)
Number achieving symptomatic remission (%)	0(0)	4(33)	2(28)	4(31)	0(0)	9(75)

developed an itchy morbilliform rash five days after entering the trial, the other developed intractable heartburn and vomiting. Both patients had been allocated SSZ and now tolerate mesalazine well.

Headaches and gastrointestinal symptoms (anorexia, nausea, vomiting, and dyspepsia) were the side effects tolerated the most. During the trial regular headaches were reported by six patients taking SSZ, four taking low dose mesalazine and five high dose mesalazine and regular upper gastrointestinal upset reported by four, four, and seven patients respectively.

On entry to the study all laboratory variables were closely matched in the three treatment groups. After four weeks treatment a small but significant fall in mean haemoglobin concentration was apparent in the SSZ treated group (entry 13.5 (1.3) g %, completion 13.0 (1.3) g %, mean (SD), $p < 0.05$). No such change was seen in either of the groups treated with mesalazine. Other haematological indices were unchanged throughout the study period although one patient receiving SSZ developed a mild leucopenia which resolved spontaneously.

Mean plasma urea and creatinine concentrations in the three groups showed no significant changes throughout the study period. Two patients allocated high dose mesalazine, however, had developed minor rises in plasma creatinine concentrations (up to two fold) on completion of the study. Neither patient had abnormalities on urine testing and both resolved spontaneously. No other significant biochemical abnormalities were apparent.

Discussion

The results of this study show that delayed release mesalazine is a useful drug in patients with active ulcerative colitis. In equivalent dose the drug was as effective, and at high dose more effective than SSZ in the treatment of mild to moderate ulcerative colitis relapse. Differences between the high dose and low dose treatment groups, however, were not statistically significant.

After four weeks treatment improvement had occurred in nine of 19 (47%) patients receiving SSZ,

15 of 20 (75%) receiving low dose, and 17 of 21 (81%) high dose mesalazine. Symptomatic remission had occurred in four of 19, six of 20, and nine of 21 patients respectively. The effects of high dose mesalazine were particularly impressive in the subgroup not taking maintenance SSZ therapy at trial onset. In this group 11 of the 12 improved, nine achieved symptomatic remission and six achieved sigmoidoscopic remission.

Several previous studies have assessed the value of oral SSZ in mild to moderate ulcerative colitis relapse. Although SSZ dose and trial designs have varied considerably clinical improvement has been reported in 65% to 80% and symptomatic remission in 25 to 52% of the groups studied.^{4-6 20 21} As these studies were undertaken in patients not receiving SSZ maintenance treatment, the results of high dose mesalazine treatment in a similar group in the present study are particularly encouraging.

The main drawback of SSZ therapy is the drug's toxicity and in the present study two patients were withdrawn because of side effects. Neither patient had been taking SSZ maintenance therapy before trial entry. No patient who received mesalazine treatment had to be withdrawn. Headaches and upper gastrointestinal upset, however, were equally matched in the three groups and other side effects were too infrequent to assess.

No major differences in haematological indices developed in the three treatment groups during the trial period although a small fall in haemoglobin concentration was apparent after SSZ treatment. Although possibly a drug related change, there was no evidence of haemolysis, reticulocytosis or macrocytosis. The fall probably reflects continuing disease activity and blood loss in the group who responded least well to treatment.

5-aminosalicylic acid has structural similarities to phenacetin and salicylic acid and both these agents have been incriminated in analgesic nephropathy.²² In addition, studies in the rat have shown that large intravenous doses of 5-ASA can cause renal tubular and renal papillary necrosis.^{23 24} In the present study, two patients developed raised creatinine concentrations after four weeks' treatment with high dose mesalazine. Both cases were asymptomatic, neither had abnormalities on urine testing and both resolved spontaneously on changing to SSZ maintenance treatment at the end of the trial. Only one other case of nephrotoxicity has appeared in the literature.²⁵ In another clinical trial, however, high dose mesalazine was found to be safe and effective over a period of 24 weeks.²⁶ In the only detailed study of renal function Diener *et al*²⁷ could find no evidence of nephrotoxicity in patients with Crohn's disease taking 1.5 g daily of a slow release 5-ASA preparation. No other

cases of renal impairment have been reported to the manufacturers, Tillotts Laboratories, although information on patients taking high dose mesalazine is still limited (personal communication). Further studies are clearly indicated and at present renal function should be closely monitored in patients taking high dose mesalazine.

Oral 5-ASA formulations not only offer the hope of improved toxicity compared with SSZ but also the possibility of greater therapeutic effect by the use of larger doses. The main advantage of delayed release mesalazine, to date, is its improved toxicity. Studies in patients unable to take SSZ because of allergic reactions or side effects have shown that the majority of patients tolerate mesalazine well although a small number do report side effects similar to those seen with SSZ.^{28,29} In addition, SSZ-induced male infertility and seminal impairment respond favourably to mesalazine substitution.³⁰ The drug is as effective as an equivalent dose of SSZ in the long-term maintenance of ulcerative colitis remission^{31,32} but unfortunately high dose studies have, as yet, failed to realise additional benefit.²⁶ Previous studies in active colitis are limited to an open uncontrolled trial of high dose mesalazine in which 67% improvement was reported after one month of treatment.²⁵

The present study shows that delayed release mesalazine in equivalent dose is as effective and in high dose appears more effective than SSZ in the treatment of mild to moderate ulcerative colitis relapse. Clinical side effects were no more common in patients treated with high dose mesalazine. In two patients raised creatinine concentrations occurred however, and this suggests the need for further toxicity studies.

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