

Clinical trial

Olsalazine or sulphasalazine in first attacks of ulcerative colitis? A double blind study

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SUMMARY Olsalazine (2 g/day) and sulphasalazine (3 g/day) were compared in a double blind three centre trial in 37 patients presenting with first attack of distal colitis. Sigmoidoscopic appearances, rectal biopsies, and symptom and stool diary records were used to assess benefit and adverse effects. Both groups showed a similar decrease in stool frequency ($p < 0.001$). The proportion of unformed stools was also decreased, but to a lesser extent ($p < 0.05$) in those taking olsalazine (78% v 55%; $p < 0.001$) compared with those taking sulphasalazine (72% v 28%; $p < 0.001$). There was a diminution in the proportion of stools containing blood in both groups (olsalazine: 61% v 22%; $p < 0.001$ /sulphasalazine: 67% v 37%; $p < 0.001$). Sigmoidoscopic and histological appearances and clinical activity improved significantly and to a similar extent in both groups. Intolerance was encountered in two patients on olsalazine and four on sulphasalazine; intolerance to sulphasalazine being even higher (five of seven patients) in a preliminary study using a dose of sulphasalazine releasing the same amount of 5-aminosalicylic acid as 2 g olsalazine. Olsalazine was at least as effective as sulphasalazine in the treatment of new patients with distal colitis, and in a dose releasing an equivalent amount of 5-aminosalicylic acid was better tolerated.

5-aminosalicylic acid has been shown to be the active therapeutic principle of sulphasalazine,¹⁻³ and is useful in the treatment of ulcerative colitis.^{1,4} Its exact mechanism of action is not known but it may act by blocking prostaglandin synthesis in the mucosa^{5,7} and/or as an anti-oxidant by suppressing oxidative metabolism of polymorphonuclear leucocytes.⁸ Olsalazine consists of two molecules of 5-ASA linked together by an azo bond.^{9,10} After oral ingestion, most of the drug reaches the colon where it is split by colonic bacteria to release 5-ASA.^{9,10}

Approximately 80% of patients intolerant of sulphasalazine can tolerate olsalazine.¹¹⁻¹³ In controlled trials of patients, a majority of whom were withdrawn from sulphasalazine, olsalazine has been shown to be superior to placebo in the treatment of

colitis¹⁴⁻¹⁶ and as effective as sulphasalazine in maintaining remission.¹⁷ Its efficacy as primary treatment, however, has not been established.

In a randomised double blind, double dummy, multicentre clinical trial, we have compared the short term efficacy and tolerance of olsalazine and sulphasalazine in new patients presenting with colitis.

Methods

PATIENTS

All patients studied were outpatient referrals with their first attack of mild or moderately severe ulcerative colitis,¹⁸ confirmed by sigmoidoscopic and histological evidence, and negative stool culture for pathogens. Patients were excluded if they had severe colitis or were considered sufficiently ill to require corticosteroids or had hepatic or renal dysfunction. The study was carried out in three centres, but

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Table 1 Details of patients at trial entry

	Olsalazine	Sulphasalazine
Patients (n)	20	17
Male:female	9:11	8:9
Mean age: years (range)	46 (19-77)	42 (21-71)
Mean duration of history: months (range)	3.7 (1-12)	4.4 (0.5-13)
Sigmoidoscopic appearance:		
Mild	3	0
Moderate	9	10
Severe	8	7
Daily stool frequency (mean (SD))	4.3 (1.9)	3.9 (1.9)

the majority of patients (32) were entered from Sheffield. The extent of disease was determined by sigmoidoscopy and/or barium enema. All of the patients had proctosigmoiditis or left sided colitis. The clinical details of the patients are shown in Table 1.

Patients were randomly allocated to receive either olsalazine or sulphasalazine along with physically indistinguishable dummies containing mainly potato starch. The drugs were provided in sealed blister packs and were taken four times a day in equally divided doses. At each visit the patients were asked to return the empty packs as a test of their compliance. The duration of the study was four weeks. At entry and at four weeks, the patients were assessed clinically and underwent sigmoidoscopy and rectal biopsy, and had blood samples taken for estimating haemoglobin, WCC, ESR, and liver biochemistry. They also provided stool samples for microbiological analysis and urine samples for analysis by dip sticks (BM-Test-5L, Boehringer). All patients were provided with diaries in which they recorded the date and time of defecation, the presence of blood and the consistency of stool (formed or unformed) and possible adverse effects. An interim clinical assessment was carried out at two weeks. Any patient who experienced an adverse effect was seen promptly and if necessary was withdrawn from the study.

Sigmoidoscopic appearance were graded as follows: normal=0, mild=1 (granular mucosa with minimal or no bleeding), moderate=2 (definite contact bleeding), severe=3 (spontaneous bleeding). The rectal biopsy specimens were examined blind by one observer (SACD) and the degree of inflammation was graded as follows: absent=0 (no evidence of inflammation), mild=1 (chronic glandular damage with definite increase in inflammatory cells), moderate=2 (changes of mild inflammation plus small foci of ulceration), severe=3 (changes of moderate inflammation plus crypt abscess formation and widespread ulceration). The clinical severity was graded using Truelove and Witts criteria.¹⁸ The

disease was considered to be in remission if the stools did not contain any blood (macroscopically), there were no more than two bowel actions per day and there was no systemic disturbance. A scoring system was used in which a change of at least one grade constituted one point which was positive for improvement and negative for deterioration. Diary information was used to determine mean daily stool frequency, the percentage of stools that were unformed, and the proportion of bloody stools during the first three days and the last three days of treatment. Overall improvement was assessed and was defined as a positive change in at least two of the following criteria: sigmoidoscopic appearances, histological appearances, clinical severity, and percentage of bloody stools.

TREATMENT REGIMEN

In a preliminary study, we carried out a double blind, double dummy comparison of 2 g olsalazine with 4 g sulphasalazine (enteric coated), administered daily in four equally divided doses. All doses for the first three days contained placebo only, and the full daily dose was attained by gradual increase over a further four days. Eleven patients were entered in this study which was terminated as a high proportion of patients had experienced intolerable adverse effects. After breaking the code it was apparent that all four patients who had received olsalazine had tolerated the drug and improved clinically. In contrast, only two of the seven patients who received sulphasalazine tolerated the drug and improved clinically, the other five having to stop the drug because of intolerable adverse effects. These were nausea and dyspepsia in three patients, headache, dizziness, and arthralgia in one patient, and a rash in one other patient. All patients except the one who developed a rash, experienced adverse symptoms only after receiving the full dose of sulphasalazine, implying that the greater number of withdrawals was caused by dose related intolerance of sulphasalazine. The study was therefore redesigned using the same dose of olsalazine (2 g/day) but a lower dose of enteric coated sulphasalazine (3 g/day). The drugs were, as before, provided in sealed blister packs and were administered four times a day, full dosage being attained gradually over seven days.

ETHICAL CONSIDERATIONS

The protocol for the study was approved by the Ethical Committee of the Sheffield Health Authority in October, 1984, and all patients gave a written informed consent.

STATISTICAL ANALYSIS

The significance of the differences in the stool

Table 2 Changes in sigmoidoscopic appearance, histological grade, clinical and overall response

	Olsalazine (n=18)	Sulphasalazine (n=13)
Sigmoidoscopic response		
Improved	15 (83%)	11 (84%)
Unchanged	3 (17%)	2 (16%)
Worse	0	0
Histological response		
Improved	8 (44%)	6 (46%)
Unchanged	10 (56%)	7 (54%)
Worse	0	0
Clinical response		
Improved	16 (89%)	10 (77%)
Unchanged	2 (11%)	3 (23%)
Worse	0	0
Overall response		
Improved	15 (83%)	9 (69%)
Worse	0	0

No significant differences between treatments.

Table 3 Influence of treatment on stool pattern

	Olsalazine (n=18)		Sulphasalazine (n=13)	
	Entry	4 weeks	Entry	4 weeks
Daily stool frequency (mean (SD))	4.4 (2.0)	2.1 (1.2)*	3.9 (1.7)	1.8 (0.6)*
Unformed stools (% of total for group)	78	55*	72	28*
Bloody stools (% of total for group)	61	22*	67	37*

*p<0.001.

frequency was determined by Student's paired *t* tests. The significance of improvement in disease gradings was determined using Wilcoxon's paired rank-sum tests. The changes in the sigmoidoscopy, rectal biopsy and clinical severity scores (Table 2) were analysed using χ^2 tests. The proportions of stools with different characteristics were compared using χ^2 tests for multiway tables.

Results

PATIENT DETAILS

Thirty nine patients were entered into the new study, of whom 21 received olsalazine and 18 received sulphasalazine. During the final analysis, one patient was excluded from each group because of non-compliance. The two groups were well matched for age and sex distribution and for severity of disease activity (Table 1).

TOLERANCE

There were no drug related haematological or biochemical abnormalities in any of our patients. Stool examination was negative for pathogens and urine analysis showed no abnormalities, except in one patient who had glycosuria at entry, and was later diagnosed as having type II diabetes mellitus.

Olsalazine

Eighteen of 20 (90%) patients tolerated this drug without any adverse effects. One patient experienced an exacerbation of diarrhoea and reported that the stools were predominantly watery rather than bloody. One other patient developed headache and nasal stuffiness. These adverse effects resolved after cessation of therapy.

Sulphasalazine

Thirteen of 17 (76%) patients tolerated this drug. Adverse effects were encountered in four patients, of whom two experienced dyspepsia and nausea, one an exacerbation of bloody diarrhoea, and one myalgia, headache, and dizziness.

The difference in tolerance between the two groups was not statistically significant ($\chi^2=0.45$).

STOOL FREQUENCY AND CONSISTENCY

There was a similar improvement ($p<0.001$) in the mean daily stool frequency in both groups of patients (Table 2). An improvement ($p<0.001$) in the proportion of unformed stools was seen in both groups of patients, but patients in the olsalazine group showed a smaller reduction ($p<0.05$) than patients in the sulphasalazine group (Table 2). There was a reduction ($p<0.001$) in the proportion of bloody stools in both groups of patients (Table 3).

SIGMOIDOSCOPIC AND HISTOLOGICAL APPEARANCES

A similar proportion of both groups of patients showed an improvement in sigmoidoscopic ($p<0.01$) and histological ($p<0.01$) appearances (Table 2).

CLINICAL IMPROVEMENT

There was an improvement in the clinical severity of disease ($p<0.001$) and overall response ($p<0.01$) in patients taking olsalazine and sulphasalazine. There was no difference in the clinical response between the two groups (Tables 2 and 3).

Discussion

Our study was unique in that none of the patients had received any other therapy for ulcerative colitis before entering the study. Previous trials have compared olsalazine with placebo in patients who were

either withdrawn from sulphasalazine¹⁴⁻¹⁶ or were intolerant of this drug.^{12,13} Similarly, a large study which compared the relapse prevention properties of olsalazine and sulphasalazine was also conducted in patients whose sulphasalazine was withdrawn.¹⁷

We have clearly shown that on the basis of clinical response, sigmoidoscopic appearance, and histological changes that both drugs were effective in inducing a remission within one month in a high proportion of patients with mild or moderately active distal ulcerative colitis. None of the patients who tolerated the drug showed a deterioration in their disease activity. The histological improvement was not as striking as the improvement in sigmoidoscopic appearances or clinical response, and is consistent with previous observations¹⁹ that there is a poor correlation between the three methods of assessment and that microscopic evidence of active disease may be seen in the absence of sigmoidoscopic or clinical evidence of activity. Hence, although histological assessment is a more accurate measurement of disease activity, therapeutic benefit assessed by histological improvement lags behind improvement in symptoms and sigmoidoscopic appearance.

Although there was a significant reduction in the proportion of stools which were unformed in both the groups, patients in the olsalazine group voided a significantly higher proportion of unformed stools compared with patients in the sulphasalazine group after but not before treatment. This may be explained by previous physiological studies which showed that olsalazine increases ileostomy output²⁰ and reduces intestinal transit time,²¹ both of which could affect stool consistency whereas sulphasalazine does not cause any such effects.^{20,22} In spite of this effect on stool consistency, there was a significant and comparable reduction in stool frequency. When assessed for clinical and overall improvement, a relatively higher proportion of patients taking olsalazine appeared to improve compared with sulphasalazine (Table 2), but this difference was not significant.

In our preliminary study we compared the two drugs using doses which released approximately equal amounts of 5-aminosalicylic acid in the colon. This study was terminated as many patients in the sulphasalazine group experienced intolerable adverse effects after receiving a daily dose of 4 g enteric coated sulphasalazine. A dose of 4-6 g sulphasalazine would have been required to produce equivalence in terms of 5-aminosalicylic acid release, to 2 g olsalazine. Moreover, even when prescribed a lower dose of sulphasalazine (3 g/day), a lower proportion of patients tolerated this drug. Thus, olsalazine was certainly better tolerated than sulphasalazine when given in comparable dosage, although

it must be pointed out that our study was conducted in patients with distal colitis and the tolerance of olsalazine in this group may be different to that of patients with total colitis.¹² In relapse prevention, which is the chief role of these drugs, it is established that 4 g sulphasalazine daily is more effective but tolerated by fewer patients than smaller doses.²³ Acceptable tolerance by most patients in our study of 2 g olsalazine, which contains approximately as much 5-aminosalicylic acid as 4 g sulphasalazine, suggests that olsalazine could be the preferable drug.

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