

A double-blind comparison of balsalazide, 6.75 g daily, and sulfasalazine, 3 g daily, in patients with newly diagnosed or relapsed active ulcerative colitis

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SUMMARY

Background: Sulfasalazine is well established in the treatment of active ulcerative colitis. Intolerance to sulfasalazine, however, is a common problem. Balsalazide has been designed to deliver 5-aminosalicylic acid to the colon without the poor tolerability of sulfasalazine.

Aim: To compare the safety and efficacy of balsalazide, 6.75 g daily, with sulfasalazine, 3 g daily, in the treatment of active ulcerative colitis of all grades of severity.

Methods: Balsalazide and sulfasalazine were compared in a multicentre, double-blind, parallel group study over 12 weeks. Patients were stratified for disease severity

and topical and/or oral steroids were co-administered where clinically necessary.

Results: Fifty-seven patients were randomized: 28 to receive balsalazide and 29 to receive sulfasalazine. Significantly fewer patients withdrew from the balsalazide group due to adverse events (2/28 vs. 9/29, $P = 0.041$). These data confirm that balsalazide is better tolerated than sulfasalazine. In patients able to tolerate the treatment, similar improvements were recorded in clinical, sigmoidoscopic and histological assessments in both treatment groups.

Conclusions: This study confirms the better tolerability of balsalazide compared to sulfasalazine, and supports the use of balsalazide in ulcerative colitis of all grades of severity.

INTRODUCTION

Sulfasalazine has an established role in the treatment of ulcerative colitis, being effective in controlling active disease and in maintaining remission.¹ Although it was first used over 50 years ago,² a recent review has argued that the additional costs of newer preparations cannot be justified in most patients, and has concluded

that sulfasalazine may still be the drug of choice for active ulcerative colitis.³

Sulfasalazine delivers 5-aminosalicylic acid to the colon by the action of colonic bacterial azo-reductase, which splits the azo-bond linking 5-aminosalicylic acid to its carrier sulfapyridine.⁴ 5-Aminosalicylic acid is believed to be the active moiety,⁵ and other methods of delivering it to the colon, including slow-release microspheres and pH-dependent coating, have been designed. In randomized trials, the newer 5-aminosalicylic acid-releasing preparations have not demonstrated superior efficacy over sulfasalazine in patients tolerant to sulfasalazine.^{3, 6–8} Most of these trials, however, have included

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sulfasalazine intolerance among the exclusion criteria, so that the real difference between the tolerability of sulfasalazine and the newer preparations is unclear. Side-effects from sulfasalazine, necessitating either a dose reduction or withdrawal, are common (up to 45%⁹) and, in a minority of patients, sulfasalazine toxicity is serious, including agranulocytosis and oligospermia.¹⁰ These side-effects are thought to be largely due to the systemic absorption of the carrier sulfapyridine.

Balsalazide is a pro-drug designed to overcome the problems associated with sulfasalazine and to deliver 5-aminosalicylic acid to the colon. It employs colonic bacterial azo-reductase to release the 5-aminosalicylic acid from the parent molecule, in a manner similar to sulfasalazine, but the carrier molecule is inert (4-aminobenzoyl- β -alanine), rather than the toxic sulfapyridine.¹¹ Balsalazide, unlike sulfasalazine, does not cause infertility, and has been shown to reverse the infertility caused by sulfasalazine;¹² it is well tolerated at high doses.¹¹

Balsalazide has been licensed for active ulcerative colitis in parts of the European Community since 1998, and in the USA since 2000. It is also licensed for, and effective in, the maintenance of remission in ulcerative colitis.^{13, 14} Previously published trials suggest that it is superior to mesalazine (5-aminosalicylic acid) delivered by a pH-dependent coating (Asacol) in achieving remission in active disease.¹⁵⁻¹⁷ Apart from one other study, using balsalazide or sulfasalazine as the sole initial therapy of mild to moderate active colitis (published in abstract form),¹⁸ there are no other data to compare balsalazide and sulfasalazine directly in patients with active ulcerative colitis.

The aims of this study were to compare the safety and efficacy of balsalazide, 6.75 g daily, with sulfasalazine, 3 g daily, in the treatment of active ulcerative colitis of all grades of severity. Patients with relapsed or newly diagnosed ulcerative colitis were included, and topical and/or oral corticosteroids were given where indicated. The study aimed to test the hypothesis that balsalazide has a significantly better tolerability than sulfasalazine. To exploit this difference, the balsalazide dose was set at 6.75 g daily, equivalent to 2.36 g of 5-aminosalicylic acid, compared to sulfasalazine, 3 g daily, equivalent to 1.15 g of 5-aminosalicylic acid. Although the dose of sulfasalazine is a lower molecular dose, this is the dose commonly used in clinical practice and was chosen to minimize the rate of intolerance to the treatment.

METHODS

Patient selection

Patients were recruited from medical gastroenterology clinics in five hospitals in the West Midlands region of the UK between July 1989 and September 1992. The protocol had the approval of the local ethics committees at each of the participating centres. Patients gave informed consent prior to entering the study. Male and female patients were recruited if they were over the age of 18 years, had sigmoidoscopically proven active ulcerative colitis (either friable or spontaneous bleeding mucosa) and a negative stool culture. Newly diagnosed and recently relapsed patients were included. In patients in whom the severity of the colitis was judged by the investigator to require treatment with topical and/or oral corticosteroids, these were also allowed. Patients were stratified for severity and therefore the use of topical and oral steroids.

Patients known to be intolerant to sulfasalazine and patients with hepatic or renal disease were excluded. Patients who were, or intended to become, pregnant during the study period were not entered into the study. Patients with a diagnosis of Crohn's disease were excluded, as were those with concomitant use of other 5-aminosalicylic acid preparations.

Study design

This was a randomized, multicentre, double-blind, parallel group study comprising balsalazide, 6.75 g daily, and sulfasalazine, 3 g daily, in the treatment of active ulcerative colitis. Randomization was stratified on the basis of the severity of relapse, which was determined by the investigator in relation to the need for additional therapy with topical and/or oral corticosteroids (mild disease = no corticosteroids; moderate disease = topical corticosteroids; severe disease = oral corticosteroids with or without topical corticosteroids).

Patients were treated for 12 weeks, with visits to the study sites at baseline, 2, 4, 8 and 12 weeks. At the first visit, a clinical history and examination were performed and a stool sample for microbiological culture was obtained. At each visit, weight, pulse, well-being, bowel frequency, stool blood, smoking, other drugs, side-effects and additional treatment with corticosteroids were recorded. The patients were given a diary in which to record stool frequency, consistency and presence of blood and/or mucus. Sigmoidoscopy was performed at

baseline and at weeks 4, 8 and 12, with rectal biopsy for histology at baseline and week 12. At entry and at the end of the trial, haematology, serum chemistry and urinalysis were performed. At the end of the study, an overall assessment was made to determine whether the patient had achieved remission. Remission was defined as a return to stool frequency (with or without pain) to that present before relapse, without the presence of blood and confirmed by biopsy.

Patients started the trial medication at full dose on the day of randomization. Study drugs were prepared, packed and labelled by Biorex Laboratories Limited, Enfield, Middlesex, UK. The trial medication was prepared in identical gelatine capsules, each containing balsalazide sodium 750 mg or sulfasalazine 333 mg triturated with lactose; patients were instructed to take three capsules three times daily.

Statistical analysis

It was envisaged that 50–60 out-patients would participate in the study. This sample size had an 80% power to detect a difference in intolerance, measured by withdrawals due to adverse events, of 35% (45% vs. 10%) at a significance level of 5%.¹⁹

The study outcome was defined in two ways: (i) remission rates at the end of the study or withdrawal; and (ii) treatment success or failure at the end of the study or withdrawal, where treatment failure was defined as any patient who withdrew or failed to attend at the end of the study, or any patient who completed the study without achieving remission. Preliminary analyses of these data were performed by logistic regression, where the stratification into mild, moderate and severe disease at the start of the study was taken into account. The stratification had no effect on the results, so that the final analysis of the remission rate and treatment outcome was performed using a chi-squared test on an intention-to-treat basis.

Signs and symptoms, and changes in signs and symptoms, were summarized by means and standard deviations or frequency tables as appropriate, and treatments were compared either by the two-sample *t*-test or by the Wilcoxon rank sum test. Changes within a treatment group were tested for significance using the Wilcoxon matched pairs signed rank test. Percentages in the frequency tables of symptoms were based on the total number of patients who had an assessment made and not on the total number of patients treated.

Side-effects were summarized using a modified World Health Organization Adverse Reaction Table; where the incidence was large enough to be compared, the comparison was made using Fisher's exact test.

RESULTS

Patients

Fifty-seven patients were recruited to the study: 28 allocated to balsalazide, 6.75 g daily, and 29 to sulfasalazine, 3 g daily. The demographic data are presented in Table 1. The stratification for disease severity ensured that there were similar numbers of patients with each severity in each treatment group (Table 1). The extent of disease was not balanced between the treatment groups with respect to proctosigmoiditis and left-sided disease. As this is unlikely to affect the study outcome, it has not been taken into account during the analysis. This was the first attack for 17/57 (30%) patients and the relapse of known disease for 40/57 (70%) patients. Of the patients recruited, 30/57 had received previous treatment with sulfasalazine

Table 1. Demographics and disease history

	Balsalazide (6.75 g/day) (n = 28)	Sulfasalazine (3 g/day) (n = 29)
Mean age (years) (s.d.)	43 (13.7)	40 (14.8)
Age range (years)	21–68	21–71
Sex (male/female)	19/9	13/16
Weight (kg) (s.d.)	72.2 (16.0)	68.3 (12.4)
Smoker (yes/no)	2/26	1/28
Disease extent		
Extensive	5	2
Left-sided	15	10
Proctosigmoid	8	16
Not known	0	1
Duration of disease (years) (s.d.)	5.0 (7.1)	4.6 (6.9)
First attack (yes/no)	6/22	11/18
Previous treatment with		
Sulfasalazine (yes/no)	14/14	16/13
5-ASA (yes/no)	8/20	8/21
Severity stratification		
Mild	8	7
Moderate	12	14
Severe	8	8

5-ASA, 5-aminosalicylic acid.

and 16/57 had received prior treatment with other 5-aminosalicylic acid preparations.

Clinical efficacy

A summary of the study outcome is presented in Table 2. There was a trend towards more patients completing the study in remission on balsalazide than on sulfasalazine (75% vs. 59%), but this was not statistically significant ($P = 0.19$). Fewer patients were withdrawn for adverse events from the balsalazide than from the sulfasalazine group (7% vs. 31%, $P = 0.041$). Details of the adverse events leading to withdrawals are shown in Table 3.

Changes in the patients' signs and symptoms were recorded at each visit. Patients' weight increased marginally in both groups (0.6 kg) over the 12-week period. The pulse rate was unchanged or showed a slight decrease in both groups. Well-being was assessed at each visit on a four-point scale ranging from normal

to unable to work. The majority of patients had their well-being at least impaired at baseline; however, slightly more patients with normal well-being were allocated to the sulfasalazine group (38% vs. 29%). The proportion of patients with normal well-being increased at each visit for both treatment groups. The entry and final visit scores are shown in Table 4. Bowel frequency was recorded on a three-point scale (0 = 0–2 per day, 1 = 3–6 per day, 2 = > 6 per day). The proportion of patients with a bowel frequency of 0–2 per day generally increased at each visit for both groups. Both treatments showed a significant improvement in stool frequency over time. Stool blood was measured on a three-point scale ranging from absent to more than a trace. As with the above markers of disease activity, the proportion of patients with no blood in their stools generally increased in both groups at each visit. The improvement in stool blood appeared to be marginally faster in the balsalazide group, with 19/27 (70%) having improved by week 2 compared to 12/26 (46%)

	Balsalazide		Sulfasalazine		<i>P</i>
	<i>n</i>	(%)	<i>n</i>	(%)	
Completed study in remission	21	(75)	17	(59)	0.19
Completed study not in remission	4	(14)	1	(3)	0.19
Withdrew adverse event	2	(7)	9	(31)	0.041
Withdrew treatment ineffective	1	(4)	1	(3)	> 0.2
Lost to follow up	0	(0)	1	(3)	> 0.2
Total	28	(100)	29	(100)	

Table 2. Study outcome

P values refer to Fisher's exact test.

Table 3. Adverse events leading to withdrawals

Drug	Day of onset	Event	Comment
Balsalazide	75	Swollen ankles	
Balsalazide	2	Diarrhoea	Event had previously occurred when patient treated with sulfasalazine and olsalazine; resolved after medication stopped
Sulfasalazine	3	Severe nausea	Subsequently treated with balsalazide
Sulfasalazine	5	Headaches and nausea	Subsequently treated with balsalazide
Sulfasalazine	1	Severe nausea	Resolved once withdrawn
Sulfasalazine	1	Severe constant headaches, bloating, abdominal and back pain	
Sulfasalazine	2	Nausea and headaches	
Sulfasalazine	1	Severe diarrhoea and passing blood	Subsequently also intolerant of balsalazide
Sulfasalazine	1	Severe heartburn and nausea	Subsequently treated with balsalazide
Sulfasalazine	12	Severe headaches	Had suffered moderate to severe headaches with sulfasalazine before
Sulfasalazine	4	Nausea and headaches	Started open label balsalazide

Table 4. Scores for well-being (0, normal; 1, impaired, but able to continue; 2, activities reduced; 3, unable to work), bowel frequency (0, 0–2 per day; 1, 3–6 per day; 2, > 6 per day) and stool blood (0, absent; 1, trace; 2, more than a trace)

	Score	Balsalazide (6.75 g/day)		Sulfasalazine (3 g/day)	
		n	(%)	n	(%)
Well-being					
Entry	0	8	(29)	11	(38)
	1	19	(68)	14	(48)
	2	0	(0)	3	(10)
	3	1	(4)	1	(3)
Week 12 (or final)	0	22	(85)	16	(89)
	1	4	(15)	2	(11)
	2	0	(0)	0	(0)
	3	0	(0)	0	(0)
Bowel frequency					
Entry	0	2	(7)	3	(10)
	1	9	(32)	13	(45)
	2	17	(61)	13	(45)
Week 12	0	16	(62)	14	(78)
	1	8	(31)	4	(22)
	2	2	(8)	0	(0)
Stool blood					
Entry	0	2	(7)	4	(14)
	1	14	(50)	14	(48)
	2	12	(43)	11	(38)
Week 12	0	20	(77)	13	(72)
	1	5	(19)	5	(28)
	2	1	(4)	0	(0)

in the sulfasalazine group by this time (between-treatment analysis, $P = 0.098$).

Sigmoidoscopies were performed at entry, 4 weeks, 8 weeks and at the final visit. The appearances were categorized on a four-point scale ranging from normal to spontaneous bleeding. The proportion of patients with normal sigmoidoscopic appearances increased at each visit for both groups (Table 5).

Rectal biopsies taken at entry and at the final visit showed similar improvements in both groups (Table 5). The proportion of patients with normal or mild inflammation increased in both treatment groups.

Corticosteroids were prescribed for patients in the moderate severity group as enemas and in the severe stratum as oral corticosteroids. Four patients in the severe group used both rectal and oral preparations (one patient allocated to balsalazide and three patients in the sulfasalazine group). As patients improved during

Table 5. Scores for sigmoidoscopic appearance (0, normal; 1, mild minimal/no bleeding; 2, contact bleeding; 3, spontaneous bleeding) and histological grade (0, normal; 1, mild ulcerative colitis; 2, moderate ulcerative colitis; 3, severe ulcerative colitis)

	Score	Balsalazide (6.75 g/day)		Sulfasalazine (3 g/day)	
		n	(%)	n	(%)
Sigmoidoscopic appearance					
Entry	0	0	(0)	0	(0)
	1	9	(32)	7	(25)
	2	18	(64)	18	(64)
	3	1	(4)	3	(11)
Week 12	0	16	(62)	12	(67)
	1	8	(31)	5	(28)
	2	2	(8)	1	(6)
	3	0	(0)	0	(0)
Histological grade					
Entry	0	0	(0)	1	(5)
	1	11	(48)	5	(23)
	2	12	(52)	14	(64)
	3	0	(0)	2	(9)
	No biopsy	5		7	
Week 12 (or final)	0	10	(50)	9	(60)
	1	8	(40)	3	(20)
	2	1	(5)	0	(0)
	3	0	(0)	1	(7)
	No biopsy	6		5	

the period of the study, corticosteroids were withdrawn. Corticosteroid use tended to decrease during the study. By the final visit, corticosteroids had been withdrawn in 11/19 (58%) patients in the balsalazide group and 11/22 (50%) patients in the sulfasalazine group.

Patient diaries

Patients recorded the consistency of their stools and whether any blood and/or mucus was passed on a daily basis in their diary cards. The information provided by patient diaries was analysed by studying 3 days at the beginning (days 0–2), middle (days 42–44) and end (days 81–83) of the study, and observing the median number of loose stools and stools with blood and mucus over this period. Diaries were not available for eight patients (two in the balsalazide and six in the sulfasalazine group). The median number of loose stools during each of the 3-day periods reduced from 12 at baseline to two at week 12 for the balsalazide group and from 10 to zero in the sulfasalazine group. The median number of

stools with blood and/or mucus decreased to zero in both treatment groups by week 6 from starting values of six for the balsalazide group and seven for the sulfasalazine group, and was maintained at this level until week 12.

The diary card data were also reviewed for the reporting of adverse events.

Adverse events

Side-effects were collected in the case report form at each visit; further adverse events were also collected following a retrospective review of the well-being of each patient, and from the final evaluation pages of the case report forms.

Serious adverse events necessitating admission to hospital were seen in two patients. One patient developed an episode of renal colic and was admitted to hospital on day 53 of the study, and the other presented with a deep vein thrombosis requiring admission on day 68. Both patients had been receiving concomitant oral prednisolone and were randomized to the balsalazide treatment arm. They both continued their study medication following their serious adverse events and completed the study in remission. It was felt that both of these adverse events were unlikely to be related to either the study medication or the corticosteroids.

Minor adverse events were common in both patient groups (balsalazide, 27/28 (96%); sulfasalazine, 27/29 (93%). The most frequently reported events were headache, abdominal pain, dyspepsia and nausea in both groups. The more frequent withdrawals due to adverse events in the sulfasalazine group (31% vs. 7%, $P = 0.041$) may indicate that these events were more severe in the sulfasalazine group. Only one of these withdrawn patients (a patient on sulfasalazine) was receiving oral corticosteroids.

The haematology and biochemistry assessment revealed no significant changes within or between the groups during the study. Urinalysis was performed at baseline and at the end of the study. No clinically significant abnormalities were observed in either treatment group.

DISCUSSION

This double-blind, randomized trial included patients with all grades of severity of ulcerative colitis. For moderate and severe disease, corticosteroids were appropriately co-prescribed. The results reveal a differ-

ence in terms of safety and patient tolerability in favour of balsalazide. Nine patients on sulfasalazine withdrew compared to two patients on balsalazide (Fishers exact test, $P = 0.041$). This difference is not supported by differences in the numbers of adverse events recorded, but it is notable that the duration of exposure to sulfasalazine was nearly one-third less than that to balsalazide because of withdrawals early in the course of treatment. Of interest, four of the nine patients intolerant to sulfasalazine subsequently settled well on balsalazide used outside the trial.

The better tolerability of balsalazide compared to sulfasalazine has been a common feature of other studies which have compared them in the acute and maintenance phases of the disease.^{13, 18} The ability of patients intolerant to sulfasalazine to tolerate balsalazide has also been documented previously in a study looking at the levels of intolerance to olsalazine, mesalazine and balsalazide.²⁰

Comparisons of efficacy between the trial drugs in this study may be confounded by the use of corticosteroids in a considerable proportion of patients. The lower proportion of sulfasalazine patients who were able to complete the study because of intolerance also affects the estimates of comparative efficacy. Stratification was carried out to ensure reasonable balance of corticosteroid use over the two treatment groups, and no subgroup analysis was intended at the outset of the study. Consequently, the numbers of patients within the mild, moderate or severe subgroups were insufficient for any useful analysis to be performed. There was a slight numerical advantage for balsalazide in remission rates (75% vs. 59%), but this was not statistically significant. Scores for individual symptoms, signs, sigmoidoscopy results and rectal histology showed that both groups improved, but did not differentiate between them. The rigorous assessment of response by sigmoidoscopic appearance and rectal histology was important to avoid any potential euphoric effect from co-administered corticosteroids.

The optimal dose and delivery method for 5-aminosalicylic acid in active colitis is controversial.²¹ Some reports suggest that very high dosages may be beneficial, while a dose-ranging study using a slow-release capsule formulation of mesalazine (5-aminosalicylic acid) has found the dose-response curve to be flat.²² In our study, it was hoped that the improved tolerability of balsalazide would enable twice the 5-aminosalicylic acid dose to be delivered to the colon, and thereby show

improved efficacy. For the reasons discussed above, the study was not powered to explore the dose–response relationship in great detail. However, the better tolerability of balsalazide was confirmed in terms of significantly fewer patients withdrawing from the study due to side-effects in the balsalazide group.

This is the only study in the literature in which balsalazide and oral corticosteroids have been co-administered. The results suggest that balsalazide is at least as suitable as sulfasalazine for concomitant use with oral corticosteroids in severely ill patients.

The use of balsalazide with topical corticosteroid enemas was a combination shown to be effective in another study of balsalazide vs. Asacol (pH-dependent mesalazine) in active mild to moderate ulcerative colitis.¹⁵ In this study, the combination has again been well tolerated and associated with a high proportion of patients entering clinical and sigmoidoscopic remission.

The use of balsalazide as sole therapy for mild disease, as in the minority of patients in this study, has been the subject of another study of balsalazide vs. sulfasalazine.¹⁸ From both studies, it seems obvious that there is a clear advantage of balsalazide in terms of tolerability, and that the treatment is effective with improvement in symptoms within 2 weeks of treatment onset. Better definition of the differences between mild and moderate disease is required to allow testing of where the thresholds for concomitant treatment with topical and oral corticosteroids should now be placed. Previous comparisons of sulfasalazine vs. corticosteroids were biased by poor sulfasalazine tolerance, as seen in this study.^{23, 24} Now that the better tolerated balsalazide is available, and the side-effects of steroids are better appreciated, the thresholds for topical and oral corticosteroid use may need to be revised.

In conclusion, in this study of relapsed and newly diagnosed active ulcerative colitis, including a full range of disease severity, balsalazide was better tolerated than sulfasalazine. Among patients able to tolerate the treatments, similar improvement rates were seen in both treatment groups.

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