hepatitis B infection interferon probably exerts its beneficial effect through the immune system, in chronic non-A non-B infection the interferon acts directly on the virus infected hepatocytes.

These initial results are encouraging, and longer term study of these patients is being undertaken to see whether the histological picture of the liver improves in parallel to biochemical values and also whether the improvement persists after interferon has been discontinued. Preliminary studies suggest that, certainly in some patients, one year of continuous treatment may be successful in bringing about a permanent biochemical and histological remission.[5] Even if relapse does occur on stopping treatment, continuous low dose interferon, which is accompanied by comparatively minor side effects, may be an acceptable inconvenience in view of the high risk of cirrhosis that untreated patients run.

We thank Sister Mary Crossey for help in managing the treatment, Jane Wadsworth for expert statistical advice, and Wellcome Research Laboratories for supplying Wellferon.

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Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial

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Abstract

***Objective*—To assess the safety and efficacy of a preparation of mesalazine (5-aminosalicylic acid) coated with a pH dependent resin (Eudragit L) as compared with sulphasalazine in patients with active mild to moderate ulcerative colitis.**

***Design*—Eight week randomised double blind parallel group study.**

***Setting*—Forty six gastroenterology outpatient clinics in seven countries.**

***Patients*—Two hundred and twenty patients aged 18-70 who met the following criteria: clinical activity index ≥6 and endoscopic index ≥4; no concomitant treatment for ulcerative colitis; no hypersensitivity to salicylates or sulphonamides. Of the 164 patients eligible for efficacy analysis, 87 received the coated preparation of mesalazine and 77 sulphasalazine. Most of the remaining patients (28 in each group) were ineligible for the efficacy analysis because of treatment with steroid enemas. All pretrial characteristics were comparable in the two treatment groups.**

***Interventions*—Coated mesalazine (Mesasal) 1·5 g daily or sulphasalazine 3·0 g daily for eight weeks. Compliance monitored by pill counts.**

***End point*—Clinical and endoscopic remission.**

***Measurements and main results*—Clinical activity measured by daily diary cards, assessment by investigators, and laboratory findings. Endoscopic evaluation at week 8. After four weeks 50 of 70 patients (71%) taking coated mesalazine and 38 of 58 (66%) taking sulphasalazine had achieved remission of their disease by eight weeks remission rates were 74% (37/50 patients) and 81% (35/43) in the two treatment groups respectively. Endoscopic remission at eight weeks was recorded in 20 of 41 patients (49%) taking coated mesalazine and 18 of 38 (47%) taking sulphasalazine. There was a higher incidence of adverse events among patients taking sulphasalazine (25/105; 24%) than among those taking coated mesalazine (16/115; 14%).**

***Conclusion*—Mesalazine coated with Eudragit L is a safe, logical alternative to sulphasalazine.**

Introduction

Sulphasalazine has been a standard treatment for acute inflammatory bowel disease and for maintaining remission since Svartz discovered its anti-inflammatory properties in the 1940s.[1-3] Its use, however, is limited by intolerance or hypersensitivity in up to one third of patients with the disease.[4-6] Sulphasalazine is composed of 5-aminosalicylic acid and sulphapyridine joined by an azo bond. 5-Aminosalicylic acid (mesalazine) is the active moiety responsible for the therapeutic efficacy of the drug in ulcerative colitis,[7-10] the sulphapyridine component (acting only as the vehicle for 5-aminosalicylic acid) evidently being responsible for most adverse effects.[11-20]

Though the exact mechanism of action is not clearly established, the anti-inflammatory properties of 5-aminosalicylic acid are apparently related to its topical effects on the inflamed colonic mucosa.[7] Inhibition of several mediators that may have a role in the pathogenesis of the inflammatory response might in part explain the therapeutic effects of 5-aminosalicylic acid. 5-Aminosalicylic acid inhibits the colonic formation of prostanoids,[21] leucotriene B_4,[22] leucotriene C_4,[23] and platelet activating factor.[24]

To maximise efficacy and minimise toxicity the logical therapeutic approach is delivery of 5-aminosalicylic acid devoid of sulphapyridine to the diseased

bowel. 5-Aminosalicylic acid is rapidly absorbed after oral ingestion and is therefore not available to act topically on the inflamed mucosa.[25] To overcome this a preparation of 5-aminosalicylic acid coated with the pH dependent methacrylate polymer Eudragit L was developed. This preparation (Mesasal; Claversal) is stable at pH concentrations of less than 6·0 and is designed to release the active component in the terminal ileum and proximal colon. A study using radiolabelling with indium to monitor transit of Mesasal through the gastrointestinal tract showed the reliability of delivery and release of 5-aminosalicylic acid.[26] The type of Eudragit coating determines the location in the gastrointestinal tract at which 5-aminosalicylic acid is released. For example, Asacol, a formulation coated with Eudragit S, releases 5-aminosalicylic acid at a pH of 7·0, so is unlikely to benefit patients with small bowel disease.[27]

This study assesses the value of the preparation coated with Eudragit L compared with sulphasalazine in patients with active mild to moderate ulcerative colitis. Throughout the report the trial preparation is referred to as coated mesalazine.

TABLE I—*Scoring systems for clinical symptoms and endoscopic findings*

	Score
Clinical activity index	
(1) No of stools weekly:	
<18	0
18-35	1
36-60	2
>60	3
(2) Blood in stools (based on weekly average):	
None	0
Little	2
A lot	4
(3) Investigator's global assessment of symptomatic state:	
Good	0
Average	1
Poor	2
Very poor	3
(4) Abdominal pain/cramps:	
None	0
Mild	1
Moderate	2
Severe	3
(5) Temperature due to colitis (°C):	
37-38	0
>38	3
(6) Extraintestinal manifestations:	
Iritis	3
Erythema nodosum	3
Arthritis	3
(7) Laboratory findings:	
Sedimentation rate >50 mm in 1st h	1
Sedimentation rate >100 mm in 1st h	2
Haemoglobin <100 g/l	4
Endoscopic index	
(1) Granulation scattering reflected light:	
No	0
Yes	2
(2) Vascular pattern:	
Normal	0
Faded/disturbed	1
Completely absent	2
(3) Vulnerability of mucosa:	
None	0
Slightly increased (contact bleeding)	2
Greatly increased (spontaneous bleeding)	4
(4) Mucosal damage (mucus, fibrin, exudate, erosions, ulcer):	
None	0
Slight	2
Pronounced	4

TABLE II—*Demographic and pretrial characteristics of patients studied. Efficacy analysis*

	Treatment group		
	Coated mesalazine (n=87)	Sulphasalazine (n=77)	Significance
No of men/No of women	55/32	48/29	0·642*
Age (years):			
Mean (SD)	38·0 (13·4)	40·4 (14·8)	0·2805†
Range	18-70	18-69	
Duration of ulcerative colitis (years):			
Mean (SD)	3·6 (4·9)	5·7 (6·8)	0·0948‡
Range	0-30	0-30	
Extent of disease (No (%) of patients):			
Rectum/sigmoid	23 (26)	20 (26)	0·297*
Partial colon	34 (39)	28 (36)	
Total colon	4 (5)	6 (8)	
Unspecified	26 (30)	23 (30)	
Disease description (No (%) of patients):			
Continuous	45 (52)	34 (44)	0·143*
Episodic	41 (47)	40 (52)	
Unspecified	1 (1)	3 (4)	
Clinical activity index:			
Mean (SD)	7·7 (2·1)	7·8 (2·1)	0·9863‡
Range	6-17	6-15	
Endoscopic index:			
Mean (SD)	8·6 (2·1)	8·7 (2·2)	0·8675‡
Range	4-12	4-12	

*Cochran-Mantel-Haenszel statistics.
†*t* Test.
‡Wilcoxon two sample test.

Patients and methods

An eight week randomised double blind parallel group study was conducted in collaboration with 46 centres in Belgium, France, Israel, Italy, Norway, South Africa, and Spain. Outpatients from gastroenterology clinics between the ages of 18 and 70 with active mild to moderate ulcerative colitis confirmed by colonoscopy were eligible. Only patients with a pretrial clinical activity index of ≥6 and an endoscopic index of ≥4 were enrolled. Table I shows the scoring systems for clinical symptoms and endoscopic findings. Criteria for exclusion from the study were pregnancy or lactation, symptoms of peptic ulcer, and concomitant treatment with oral and rectal corticosteroids, immunosuppressives, metronidazole, and sodium cromoglycate. In addition, patients with disease confined to the rectum, disease of bacterial origin, or toxic megacolon were not eligible. Other criteria for exclusion included colonic malignancy, abnormal laboratory values, and known hypersensitivity to salicylates or sulphonamides.

At the pretrial visit, in addition to medical history, physical examination, and colonoscopy, the patient's baseline disease state was scored. This index encompassed data from the previous week and included number of stools weekly, amount of blood in stools, abdominal pain or cramps, physician's assessment of patient's condition, body temperature, extraintestinal manifestations, erythrocyte sedimentation rate, and haemoglobin concentration. After written or oral informed consent was obtained eligible patients were dispensed either coated mesalazine (Mesasal) 1·5 g daily or sulphasalazine 3·0 g daily in a double blind manner using a double dummy technique. Drug supplies were centrally packaged, labelled, and randomised in blocks of four according to a predetermined list generated by a computer. Patients were instructed to begin treatment that day, to record symptoms on daily diary cards, and to return at two week intervals. A symptomatic assessment was completed at each bi-weekly follow up visit and mandatory repeat colonoscopy performed at the completion of eight weeks. Laboratory studies including complete blood count, liver and kidney function tests, and urine analysis were performed at each visit.

Statistical methods—The two treatment groups were compared with respect to demographic and pretrial assessment variables. A clinical activity index of ≤4 during the study was taken as the main evidence of remission in the analysis of efficacy. Remission rates (prevalence rates) at each assessment period and the 95% confidence intervals were calculated and analysed for treatment differences by using Cochran-Mantel-Haenszel statistics controlling for effects of individual centres on both the intention to treat and evaluable populations of patients. Each component of the clinical activity index was analysed for treatment differences by the statistical methods described above. The mean clinical activity index and mean endoscopic index were analysed by the Wilcoxon rank sum test controlling for

TABLE III—*Demographic and pretrial characteristics of patients studied. Intention to treat analysis*

	Treatment group		
	Coated mesalazine (n=115)	Sulphasalazine (n=105)	Significance
No of men/No of women	71/44	61/44	0·365*
Age (years):			
Mean (SD)	38·7 (12·9)	39·5 (14·5)	0·6807†
Range	18-70	18-69	
Duration of ulcerative colitis (years):			
Mean (SD)	4·4 (5·7)	5·6 (6·4)	0·2029‡
Range	0-30	0-30	
Extent of disease (No (%) of patients):			
Rectum/sigmoid	32 (28)	26 (25)	
Partial colon	42 (37)	38 (36)	0·221*
Total colon	5 (4)	9 (9)	
Unspecified	36 (31)	32 (30)	
Disease description (No (%) of patients):			
Continuous	56 (49)	43 (41)	
Episodic	57 (50)	59 (56)	0·062*
Unspecified	2 (2)	3 (3)	
Clinical activity index:			
Mean (SD)	7·8 (2·3)	8·0 (2·5)	0·8604‡
Range	3-17	5-15	
Endoscopic index:			
No studied	107	95	
Mean (SD)	8·5 (2·1)	8·7 (2·2)	0·4975‡
Range	4-12	4-12	

*Cochran-Mantel-Haenszel statistics. †*t* Test. ‡Wilcoxon two-sample test.

effects of different countries and using pretrial values as a covariate.

Results

Of the 220 patients who entered the trial, 164 were considered eligible for the analysis of efficacy. There were no differences between treatments with respect to pretrial characteristics when all patients (intention to treat) or evaluable patients were compared (tables II and III). Fifty six patients (28 in each treatment group) were excluded because of default or violations of protocol, treatment with steroid enemas being the main reason for exclusion (table IV). As a large proportion of patients in each treatment group failed to complete eight weeks (table V) or were not considered eligible for the analysis of efficacy, an intention to treat analysis was performed in addition to the main analysis.

TABLE IV—*Reasons for excluding patients from analysis of efficacy*

Reason for exclusion	No of patients	
	Coated mesalazine treatment group (n=115)	Sulphasalazine treatment group (n=105)
Default*	5	1
Clinical activity index <6	3	3
Ulcerative colitis confined to rectum	1	
Non-compliance†	4	9
Patient request		1
Treatment with corticosteroid enemas	15	14
Total	28	28

*Default=violated study protocol.
†Non-compliance=did not take study medication as instructed—that is, took fewer than 80% of prescribed tablets.

TABLE V—*Reasons for early withdrawal from trial*

Reason for early withdrawal	No of patients	
	Coated mesalazine treatment group	Sulphasalazine treatment group
Adverse event	7	8
Default*	4	2
Insufficient therapeutic effect	16	12
Non-compliance†	8	11
Patient's request	3	3
Total	38	36

*Default=violated study protocol.
†Non-compliance=took less than 80% of study medication; failed to attend for follow up visits.

RESPONSE TO TREATMENT

In both treatment groups a mean clinical activity index of ≤4 (remission) was achieved by week 4. The index remained below 4 in both groups for the remaining four weeks (table VI). The proportion of patients receiving each treatment who achieved remission was similar at each assessment period, and by week 4, 50 of 70 patients (71%) taking coated mesalazine and 38 of 58 (66%) taking sulphasalazine were in remission (p=0·338) (table VII). After eight weeks 37 of 50 patients (74%) and 35 of 43 patients (81%) (p=0·835), respectively, had achieved remission. Of those who did not achieve remission, a similar proportion (14%) in each group experienced improvement (reduction) in their clinical activity index. Remission rates evaluated in all patients (intention to treat) showed no significant differences between treatments (week 8, p=0·786) (table VIIIm (miniprint)). In addition, the proportion of these patients in remission was similar to the proportion in remission in the analysis of efficacy.

TABLE VI—*Mean clinical activity index*

	Treatment group		Significance (Wilcoxon rank sum test)
	Coated mesalazine	Sulphasalazine	
Before trial:			
No studied	86	77	
Mean	7·7	7·8	
SD	2·1	2·1	
Median	7·0	7·0	
Range	6-17	6-15	
Week 2:			
No studied	82	71	
Mean	5·2	5·1	
SD	3·1	3·5	0·5789
Median	5·0	4·0	
Range	0-16	0-17	
Week 4:			
No studied	70	58	
Mean	3·8	3·7	
SD	3·6	2·8	0·5249
Median	3·0	3·0	
Range	0-21	0-11	
Week 6:			
No studied	60	48	
Mean	3·2	2·8	
SD	2·8	2·7	0·6592
Median	3·0	2·0	
Range	0-12	0-10	
Week 8:			
No studied	50	43	
Mean	3·1	2·7	
SD	3·3	3·1	0·8088
Median	2·0	2·0	
Range	0-13	0-14	

The proportion of patients reporting fewer than 18 bowel movements a week increased at each assessment period from roughly 7% before the trial to over 50% by week 8 (p=0·761) for both groups (table IXm). After eight weeks of treatment 26 of 50 patients (52%) taking the coated preparation and 25 of 43 (58%) (p=0·993) taking sulphasalazine reported absence of blood in their stools (table Xm). The quality of stools also improved throughout the study in both treatment groups (table XIm). A significant difference (p=0·048) in favour of sulphasalazine was detected at week 2, but by week 4 and for the remainder of the trial the incidence of patients reporting normal consistency of stools was similar in the two groups. No significant difference was detected between the two groups with respect to the number of patients suffering abdominal pain or cramps. The proportion of patients without pain increased during the trial in both groups, and by the end of eight weeks 31 of 50 patients (62%) taking coated mesalazine and 28 of 43 (65%) (p=0·438) taking sulphasalazine were pain free (table XIIm).

After eight weeks the mean (SD) pretrial endoscopic index decreased from 8·6 (2·1) to 5·2 (3·6) in patients taking the coated preparation and from 8·7 (2·2) to 4·3 (3·5) in those treated with sulphasalazine. Of patients in the two groups subjected to endoscopy after eight

TABLE VII—*Remission rates (evidence of remission taken as a clinical activity index ≤4)*

	Treatment group: Coated mesalazine	Treatment group: Sulphasalazine	Significance (Cochran-Mantel-Haenszel statistics)
Week 2:			
Patients treated	82	71	0·722
No (%) in remission	39 (48)	38 (54)	
95% Confidence interval (%)	37·1 to 58·2	42·0 to 64·6	
Week 4:			
Patients treated	70	58	0·338
No (%) in remission	50 (71)	38 (66)	
95% Confidence interval (%)	59·9 to 80·6	52·6 to 76·4	
Week 6:			
Patients treated	60	48	0·859
No (%) in remission	41 (68)	36 (75)	
95% Confidence interval (%)	55·7 to 78·6	61·2 to 85·0	
Week 8:			
Patients treated	50	43	0·835
No (%) in remission	37 (74)	35 (81)	
95% Confidence interval (%)	60·4 to 84·1	67·3 to 90·2	

weeks of treatment, 20 of 41 (49%) and 18 of 38 (47%) respectively had endoscopic scores of less than 4 (p= 0·272) (table XIII).

Of the patients who discontinued the trial before completion, 16 (18%) in the coated mesalazine treatment group and 12 (16%) in the sulphalazine treatment group did so because of inefficacy of treatment (table V).

ADVERSE EFFECTS

The most frequently occurring adverse events were hypersensitivity reactions—for example, pruritus and rash—headache, nausea and vomiting, and epigastric and abdominal pain. Though the incidence of headache and abdominal and epigastric pain was similar in the two treatment groups, four times as many patients taking sulphasalazine had hypersensitivity reactions and episodes of nausea and vomiting (table XIV). Overall only 16 patients (14%) in the coated mesalazine treatment group suffered adverse events as compared with 25 (24%) in the group given sulphasalazine (table XV). Seven patients (6%) treated with coated mesalazine and 8 (8%) given sulphasalazine were withdrawn from the trial because of adverse events. Six of the eight patients withdrawn from the sulphasalazine treatment group had hypersensitivity reactions (rash, pruritus, angioneurotic oedema), two needing admission to hospital. By contrast, only one patient taking coated mesalazine had to stop treatment because of pruritus. The remaining two patients withdrawn from the sulphasalazine treatment group suffered gastrointesti-

TABLE XIII—*Endoscopic remissions at week 8*

	Treatment group: Coated mesalazine	Treatment group: Sulphasalazine	Significance (Cochran-Mantel-Haenszel statistics)
Patients treated	41	38	0·272
No (%) in remission	20 (49)	18 (47)	
95% Confidence interval (%)	34·2 to 63·5	32·4 to 62·7	

TABLE XIV—*Incidence of most frequently occurring adverse events. Figures are numbers (percentages) of patients*

Adverse event	Treatment group: Coated mesalazine (n=115)	Treatment group: Sulphasalazine (n=105)
Hypersensitivity reactions (rash, pruritus, etc)	3 (2·6)	12 (11·4)
Nausea/vomiting	2 (1·7)	8 (7·6)
Headache	4 (3·5)	5 (4·8)
Abdominal/epigastric pain	5 (4·3)	3 (2·9)

TABLE XV—*Incidence of adverse events stratified by body system affected*

Body system	No of patients: Coated mesalazine treatment group	No of patients: Sulphasalazine treatment group
General:		
Eosinophilia	1	–
Fever	1	3
Fatigue	1	–
Central nervous system:		
Headache	4	5
Paraesthesia	–	2
Gastrointestinal:		
Abdominal/epigastric pain	5	3
Diarrhoea	1	–
Heartburn	–	2
Mouth dryness	–	1
Nausea/vomiting	2	8
Stomatitis	1	–
Hepatic:		
Cholestasis	1	–
Hepatitis	1	–
Hepatomegaly/jaundice	–	1
Raised liver function values	1	3
Musculoskeletal:		
Joint pain/myalgia	4	–
Psychiatric:		
Depression	1	–
Reproductive:		
Irritation in penis	1	–
Premenstrual oedema	–	1
Respiratory:		
Dyspnoea	1	–
Skin:		
Angioneurotic oedema	–	2
Erythema/rash	1	9
Pruritus	2	6
Urinary:		
Serum creatinine increased	–	1
Total events*	29	47
Total No (%) of patients with events	16 (14)	25 (24)
Total population	115	105
Total No (%) of patients withdrawn because of events	7 (6)	8 (8)

*Some patients experienced more than one event.

MINIPRINT TABLES VIII-XII

VIII

TABLE VIII—*Remission rates. Intention to treat analysis*

	Treatment group: Coated mesalazine	Treatment group: Sulphasalazine	Significance (Cochran-Mantel-Haenszel statistics)
Week 2:			
Patients treated	105	96	0·823
No (%) in remission	49 (47)	47 (49)	
95% Confidence interval (%)	37·4 to 56·1	39·1 to 58·8	
Week 4:			
Patients treated	90	84	0·090
No (%) in remission	65 (72)	52 (62)	
95% Confidence interval (%)	62·2 to 80·4	51·2 to 71·5	
Week 6:			
Patients treated	82	76	0·811
No (%) in remission	57 (70)	54 (71)	
95% Confidence interval (%)	58·8 to 78·4	60·0 to 80·0	
Week 8:			
Patients treated	77	69	0·786
No (%) in remission	59 (77)	53 (77)	
95% Confidence interval (%)	66·0 to 84·6	65·6 to 85·1	

IX

TABLE IX—*Frequency of stools weekly. Figures are numbers (percentages) of patients*

	Treatment group: Coated mesalazine	Treatment group: Sulphasalazine	Significance (Cochran-Mantel-Haenszel statistics)
Before trial:			
<18	7 (8·1)	5 (6·5)	0·379
18-35	40 (46·5)	29 (37·7)	
36-60	23 (26·7)	33 (42·9)	
>60	16 (18·6)	10 (13·0)	
Week 2:			
<18	21 (25·6)	23 (32·4)	*
18-35	34 (41·5)	27 (38·0)	0·870
36-60	21 (25·6)	16 (22·5)	
>60	6 (7·3)	5 (7·0)	
Week 4:			
<18	33 (47·1)	27 (46·6)	0·282
18-35	22 (31·4)	22 (37·9)	
36-60	9 (12·9)	9 (15·5)	
>60	6 (8·6)		
Week 6:			
<18	29 (48·3)	26 (54·2)	0·773
18-35	18 (30·0)	15 (31·3)	
36-60	9 (15·0)	6 (12·5)	
>60	4 (6·7)	1 (2·1)	
Week 8:			
<18	28 (56·0)	23 (53·5)	0·761
18-35	11 (22·0)	13 (30·2)	
36-60	7 (14·0)	5 (11·6)	
>60	4 (8·0)	2 (4·7)	

X

TABLE X—*Blood in stools. Figures are numbers (percentages) of patients*

	Treatment group: Coated mesalazine	Treatment group: Sulphasalazine	Significance (Cochran-Mantel-Haenszel statistics)
Before trial:			
None	1 (1·2)	2 (2·6)	0·569
Little	51 (59·3)	41 (53·2)	
A lot	34 (39·5)	34 (44·2)	
Week 2:			
None	19 (23·5)	25 (35·2)	0·207
Little	44 (54·3)	38 (53·5)	
A lot	18 (22·2)	8 (11·3)	
Week 4:			
None	24 (34·3)	28 (48·3)	0·575
Little	42 (60·0)	26 (44·8)	
A lot	4 (5·7)	4 (6·9)	
Week 6:			
None	24 (40·0)	29 (60·4)	0·204
Little	33 (55·0)	17 (35·4)	
A lot	3 (5·0)	2 (4·2)	
Week 8:			
None	26 (52·0)	25 (58·1)	0·993
Little	20 (40·0)	16 (37·2)	
A lot	4 (8·0)	2 (4·7)	

XI

TABLE XI—*Quality of stools. Figures are numbers (percentages) of patients*

	Treatment group: Coated mesalazine	Treatment group: Sulphasalazine	Significance (Cochran-Mantel-Haenszel statistics)
Before trial:			
Normal	4 (4·7)	4 (5·2)	0·379
Soft	37 (43·0)	27 (35·1)	
Liquid	43 (50·0)	45 (58·4)	
Other	2 (2·3)	1 (1·3)	
Week 2:			
Normal	16 (19·5)	16 (22·5)	0·480*
Soft	33 (40·2)	42 (59·2)	
Liquid	33 (40·2)	13 (18·3)	
Week 4:			
Normal	25 (35·7)	29 (50·0)	NS
Soft	27 (38·6)	22 (37·9)	
Liquid	17 (24·3)	7 (12·1)	
Other	1 (1·4)		
Week 6:			
Normal	25 (41·7)	30 (62·5)	0·327
Soft	27 (45·0)	14 (29·3)	
Liquid	7 (11·7)	4 (8·3)	
Other	1 (1·7)		
Week 8:			
Normal	29 (58·0)	26 (61·9)	0·726
Soft	15 (30·0)	11 (26·2)	
Liquid	6 (12·0)	5 (11·9)	

NS = Not significant.

XII

TABLE XII—*Abdominal pain or cramps. Figures are numbers (percentages) of patients*

	Treatment group: Coated mesalazine	Treatment group: Sulphasalazine	Significance (Cochran-Mantel-Haenszel statistics)
Before trial:			
None	10 (11·6)	8 (10·4)	0·581
Mild	43 (50·0)	33 (42·9)	
Moderate	31 (36·0)	32 (41·6)	
Severe	2 (2·3)	4 (5·2)	
Week 2:			
None	30 (36·6)	27 (38·0)	0·744
Mild	39 (47·6)	33 (46·5)	
Moderate	13 (15·9)	10 (14·1)	
Severe		1 (1·4)	
Week 4:			
None	33 (47·1)	24 (41·4)	0·116
Mild	33 (47·1)	29 (50·0)	
Moderate	2 (2·9)	5 (8·6)	
Severe	2 (2·9)		
Week 6:			
None	32 (53·3)	29 (60·4)	0·438
Mild	23 (38·3)	14 (29·2)	
Moderate	3 (5·0)	4 (8·3)	
Severe	2 (3·3)	1 (2·1)	
Week 8:			
None	31 (62·0)	28 (65·1)	0·438
Mild	18 (36·0)	13 (30·2)	
Moderate		2 (4·7)	
Severe	1 (2·0)		

nal events (vomiting, which necessitated admission, and epigastric pain). Of the seven patients withdrawn from coated mesalazine, one was admitted to hospital for acute pancreatitis after two days of treatment. Other events necessitating withdrawal of coated mesalazine were upper gastrointestinal complaints (nausea, epigastric pain), headache, eosinophilia, muscle fatigue, increased liver function values, and cholestasis.

Discussion

The aetiology of ulcerative colitis remains unknown and the goal of treatment is to control the inflammatory process without causing serious side effects. In this trial of a new, enteric coated preparation of mesalazine versus sulphasalazine patients with mild to moderately active disease achieved similar rates of remission (as measured clinically and endoscopically) after eight weeks of treatment. In addition, similar proportions of patients discontinued treatment because of therapeutic inefficacy. Coated mesalazine, however, was associated with substantially fewer adverse effects than recorded with sulphasalazine, patients in the sulphasalazine treatment group having four times as many hypersensitivity type reactions and episodes of nausea and vomiting.

We did not address the question whether patients intolerant of sulphasalazine can tolerate coated mesalazine. Cumulative data, however, suggest that most of these patients tolerate mesalazine, though a few may experience the same side effects.[28-34]

The therapeutic efficacy of 1·5 g coated mesalazine daily was similar to that of sulphasalazine 3·0 g daily. Clinical improvement or remission of mild to moderate exacerbations of disease was achieved in 86%,[35] 81%,[36] and 72%[37] of patients after four to seven weeks' treatment with 2·4 g daily of mesalazine coated with Eudragit S. When a high dose (4·8 g/day) regimen of this preparation was compared with placebo pronounced efficacy and excellent tolerance were recorded in patients with mild to moderately active disease.[28] Olsalazine, another therapeutic modality designed to deliver 5-aminosalicylic acid to the colon, was shown to be valuable in mildly active ulcerative colitis[32] and for maintaining remission.[33] Though this compound was well tolerated by patients intolerant of or allergic to sulphasalazine, it induced diarrhoea necessitating withdrawal in about 10% of patients.[33] Higher doses of mesalazine coated with Eudragit L may prove to be even more efficacious, and clinical trials with doses up to 4·0 g daily are warranted. We conclude that in patients with active mild to moderate ulcerative colitis the coated preparation of mesalazine as used in this trial is a safe, effective treatment.

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