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Prophylactic effects of olsalazine *v* sulphasalazine during 12 months maintenance treatment of ulcerative colitis

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Abstract

In a Danish multicentre trial we compared the relapse preventing effects of olsalazine and sulphasalazine in patients with ulcerative colitis over a 12 month treatment period. Two hundred and twenty seven patients (118 men) with at least two previous attacks of ulcerative colitis were randomly allocated according to a prearranged treatment schedule to olsalazine 500 mg bd or sulphasalazine 1 g bd in a double blind, double dummy fashion. One hundred and ninety seven patients completed the trial. The relapse rate after 12 month in the olsalazine group was 46·9% *v* 42·4% in the sulphasalazine group with a 95% confidence interval for the difference in proportions of −9% to 18%. Seven per cent of the patients were withdrawn from the trial because of adverse drug reactions and these were equally distributed between the two groups.

Sulphasalazine is widely accepted as the drug of choice for ulcerative colitis, for maintenance of remission and for treatment of mild attacks.

Over a six month period patients receiving sulphasalazine (2 g) had less than one quarter (<25%) the relapse rate of those receiving placebo.[1]

Unfortunately, sulphasalazine can cause a varied spectrum of adverse effects in 10–45% of those who are dependent upon it.[2] The active therapeutic moiety of sulphasalazine is 5-ASA while sulphapyridine functions as a carrier ensuring that the 5-ASA is liberated within the colon.[3] As the majority of the adverse events of sulphasalazine are ascribed to the sulphapyridine moiety,[4] extensive investigations into alternative ways of delivering 5-ASA to the colon have been carried out. Olsalazine (Dipentum) is a drug composed of two 5-ASA molecules linked together through an azo bond. The drug effectively releases two molecules of 5-ASA upon azo reduction in the colon.[5] Olsalazine is of proven value in patients intolerant of sulphasalazine,[6 7] and is also effective in patients with a mildly active ulcerative colitis.[8] Olsalazine has been shown superior to placebo in maintaining remission in patients with ulcerative colitis over a six month period.[6] A recent study has shown that olsalazine is as effective as sulphasalazine for the maintenance treatment of ulcerative colitis over a six month period.[9]

The aim of the present study was to evaluate the relapse preventing effect of olsalazine compared with sulphasalazine over a one year period in patients with ulcerative colitis in remission.

Methods

PATIENTS

From March 1988 to May 1989 227 outpatients with ulcerative colitis in remission were randomised to treatment with either olsalazine 500 mg bd or sulphasalazine 1 g bd for one year in a double blind, double dummy, Danish multicentre study. Patients were instructed to take their medication with meals (breakfast and dinner). Only patients with a medical history of at least two attacks of ulcerative colitis were included in the study, and the age of the patients were between 18 and 80 years. Remission was defined by: (i) no visible blood in the stools for more than three days within the last week, and/or (ii) less than three stools per day for at least four days within the last week, and (iii) sigmoidoscopy grade 1–2 at admission (no spontaneous bleeding without or with distinct vessels in the mucosa). Patients were excluded from the trial if they had shown hypersensitivity to sulphonamides or salicylates, were pregnant or were planning pregnancy within a year, or had received cystostatic or corticosteroid treatment within the last month before entry.

The randomisation was computer generated, stratified for each centre and performed in blocks of four consecutive patients within centre. Twelve centres participated including from 10 to 39 patients. The patients were initiated on medication immediately after randomisation. The patients were seen at three monthly intervals throughout the study. Clinical examination, sigmoidoscopy and blood tests (haematological,

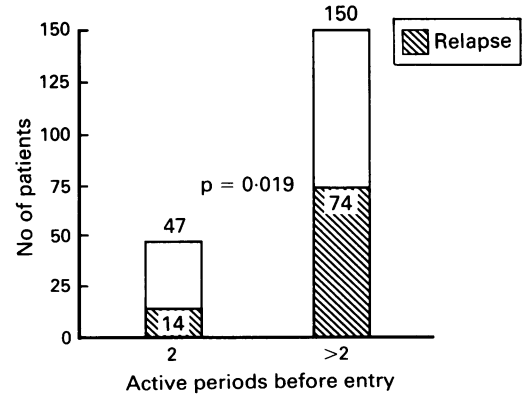

Figure 1: Relapse frequency in relation to number of active periods of the disease before entry.

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liver and renal function tests) was done before entry and after six and 12 months or at exit from the study. At each visit the number of consumed tablets were questioned. Patients ended the study after 12 month treatment or in case of relapse. They were withdrawn from the study if any side effect occurred which necessitated stopping therapy. Relapse was defined as inflammation of the rectal mucosa grade 3–4 on sigmoidoscopy (no distinct vessels in the mucosa, spontaneous bleeding and bleeding by contact with the sigmoidoscope).

Olsalazine was delivered in enteric coated tablets. Yellow 500 mg olsalazine sodium tablets coated with 50/50 of Eudragit® L+S to disintegrate in vitro at pH 6·5. Not less than 85% of the olsalazine sodium is released within 120 minutes in buffer solution pH 6·8.

STATISTICAL ANALYSIS AND ETHICS

The sample size was based on the assumption that the true relapse rate was 20% in sulphasalazine treated patients with alpha 5%, beta 20%, and the difference in relapse rate between treatment of interest to detect equal to 20% units. The calculated number of patients required in each group was 83. In order to allow for patients unable to be evaluated a total number of 214 patients was planned to be included in the study.

The treatment groups were compared with regard to relapse rate by use of Pearson χ^2 test, and a 95% confidence interval for the difference in relapse rate. The life-table was estimated by the Kaplan-Meyer method, and the logrank test to compare the survival curves.

The study was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all the patients, and the study was approved by the Regional Ethical Committees of the participating hospitals.

Results

Among the 227 patients included in the study, one patient on revision was found not to fulfil the inclusion criteria and a further three patients were lost to follow up. This left 223 patients for intention to treat analysis. Of these 15 patients were withdrawn because of adverse drug events (including the patient who did not fulfil the inclusion criteria) (Table I), two patients because of intercurrent unrelated disease (one acute appendicitis, one cancer of the colon), nine patients because of non-compliance (four in the olsalazine and five in the sulphasalazine group), and, finally, one because of an incomplete case record form. That left 197 patients for per protocol analysis.

Table II shows that both groups were evenly matched for patient and disease characteristics. The rates of remission and relapse according to per protocol analysis in the olsalazine and the sulphasalazine treated groups are shown in Table III, and Table IV shows the distribution between remission and failures according to the intention-to-treat analysis in the two groups. The relapse rate after 12 month in the olsalazine group is

TABLE I *Withdrawals caused by adverse drug events*

Adverse drug events	*Patients receiving OLZ*	*SASP*
Diarrhoea	5	2
Loose stools	1	0
Abdominal pain	1	0
Constipation	2	0
Urticaria	0	1
Nausea	0	1
Dyspepsia	0	2
Total	9	6

OLZ=olsalazine, SASP=sulphasalazine.

TABLE II *Patient and disease characteristics*

	OLZ	*SASP*
n	114	112
Age (yr)		
mean	41·4	39·6
range	20–79	18–75
Sex		
males	56	62
females	58	50
Weight (kg)		
mean	71	73
range	38–113	51–106
Height (cm)		
mean	171	173
range	150–193	141–199
Duration of UC (yr)		
mean	9·1	8·4
range	0·3–37	0·4–38
Extent of disease		
proctitis	59	55
proctocolitis	54	57
Number of active periods before entry		
2	25	30
>2	89	82
Duration of remission (month)		
mean	15	11
range	6–321	2–152
SASP on entry	91	91

OLZ=olsalazine, SASP=sulphasalazine, UC= ulcerative colitis.

46·9% *v* 42·4% in the sulphasalazine group with a 95% confidence interval for the difference in proportions of −9% to 18%. In the combined groups (olsalazine+sulphasalazine the relapse rate in patients with more than two active periods were higher than in patients with two active periods (49% *v* 30% p=0·02). From the life-table (Fig 2) it appears, that the cumulative relapse rate is similar in both groups, and that the time span from entry into the study to relapse is similar in each group (p=0·54).

There was no relation between relapse frequency and the extent of the disease or of a remission period of more or less than three months. There were no clinically significant alterations in any of the haematological or biochemical variables as measured from the blood tests in either of the two groups.

Discussion

For many years sulphasalazine has been the mainstay of relapse preventing therapy in ulcerative colitis.[10] Previously olsalazine was found superior to placebo as a maintenance agent,[6] and in the present double blind controlled study we have shown that olsalazine was equally effective as sulphasalazine. In both treatment groups remission was maintained throughout a year in a little more than half of the patients. The high number of patients incorporated in our investigation yields a low risk of clinically significant type 2 error. Our study confirms and extends the findings of Ireland *et al*,[9] who used the same

dosages of sulphasalazine and olsalazine. They found, however, a lower half year relapse rate than we did. The reason is likely to be that the patients in their study had a remission of at least six months before entering the study compared with only one month in this study. Furthermore, our patients had a relatively high tendency to recurrence as we only included patients with a medical history of at least two previous attacks of ulcerative colitis.

We did not include histological assessment of rectal biopsies in our evaluation of disease activity. The reason was that there is a poor correlation between histological appearance and clinical sigmoidoscopic state.[11] Histological improvement lags behind improvement in symptoms and sigmoidoscopic appearance,[6] and histological relapse precedes clinical deterioration.[8]

Several studies, mostly in patients intolerant of sulphasalazine, have shown that olsalazine is superior to placebo in the treatment of mild to moderately active ulcerative colitis.[8 12-14] In a few investigations olsalazine was compared with sulphasalazine.[15 16] No difference in drug efficacy could be detected. These studies comprised relatively few patients, however, and this is why minor differences in effect rate could easily be overlooked. Seven per cent of the patients were withdrawn from the trial because of adverse drug reactions. The events were minor and their incidence was the same in the two treatment groups. Patients who previously were found intolerant of sulphasalazine were excluded from the study. This resulted in a selection of patients which with regard to side effects was in favour of sulphasalazine. The tolerability of olsalazine may therefore be even more favourable. In a study of patients presenting with first attack of ulcerative colitis Rao *et al* found that olsalazine was better tolerated than sulphasalazine in doses releasing equal amounts of 5-ASA.[16]

Diarrhoea is the most common side effect of olsalazine, occurring in some studies with a frequency of 12%[6 9] or greater.[14] The occurrence of diarrhoea is a dose related event and it is more common in patients with extensive colitis.[6] Experiments in animals and in human ileostomy patients have shown that olsalazine acts as a secretagogue in the small intestine increasing the fluid load to the colon.[17-20] An acceleration of gastrointestinal transit may partly be responsible for the diarrhoea.[21] Only 5% of our patients treated with olsalazine complained of diarrhoea (three with proctitis and two with proctisigmoiditis). That was marginally more than among those who received sulphasalazine, and the difference was not significant. The low incidence of diarrhoea may reflect the low dosage of olsalazine used and the limited extent of the colitis exhibited in the majority of patients. Furthermore, an enteric coated tablet formulation of olsalazine was used here compared with a gelatine capsule in the study by Ireland.[9]

We conclude that olsalazine 500 mg bd is equally effective and has the same incidence of adverse reactions as sulphasalazine 1 g bd in the maintenance therapy of ulcerative colitis. Because patients who previously were found intolerant of sulphasalazine were excluded from the study, olsalazine may in fact be more tolerable.

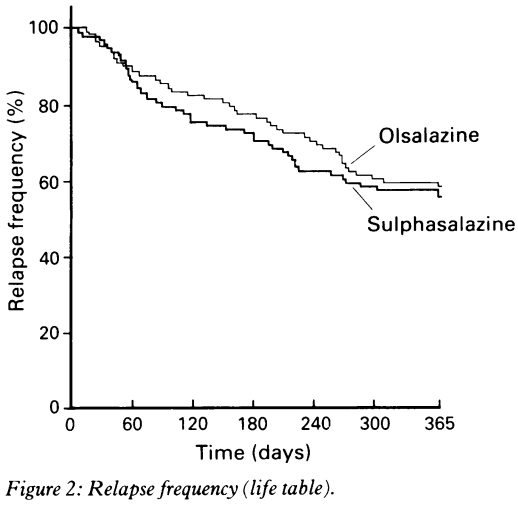

Figure 2: Relapse frequency (life table).

TABLE III *Relapse rate according to per protocol analysis*

	Olsalazine	*Sulphasalazine*	*Total*
Remission	52	57	109
Relapse	46	42	88
Total	98	99	197

χ^2 p=0·524
Relapse rate (95% confidence limits)
OLZ: 46·9% (37%–57%)
SASP: 42·4% (33%–52%)
Difference OLZ-SASP 4·5% (−9% −18%).

TABLE IV *Failure rate according to intention-to-treat analysis*

	Olsalazine	*Sulphasalazine*	*Total*
Remission	53	57	110
Failure	60	53	113
Total	113	110	223

χ^2 p=0·463
Failure rate (95% confidence limits)
OLZ: 53·1% (44%–62%)
SASP: 48·2% (39%–58%)
Difference OLZ-SASP 4·9% (−8% −18%).

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