CLINICAL RESEARCH

Olsalazine in active ulcerative colitis

W S SELBY, G D BARR, A IRELAND, C H MASON, D P JEWELL

Abstract

Olsalazine (azodisalicylate) is a new drug in which two molecules of 5-aminosalicylic acid are linked by an azo bond. Its role in the treatment of mildly active, distal ulcerative colitis was investigated. Sixty patients were randomly allocated to receive olsalazine 1 g or a placebo as a retention enema nightly for two weeks. Clinical improvement was seen in 19 (66%) and sigmoidoscopic improvement in 17 (59%) of the 29 patients receiving olsalazine compared with 12 (43%) and 11 (39%), respectively, of the 28 in the control group. These differences were not significant. In a second trial 40 patients were randomised to receive oral olsalazine 2 g daily or a placebo capsule for two weeks. Significant clinical and sigmoidoscopic improvement was seen in the patients receiving oral olsalazine compared with the patients receiving placebo capsules.

Oral olsalazine may be valuable in the treatment of mildly active ulcerative colitis. Its role in maintaining remission is yet to be determined.

Introduction

Sulphasalazine is effective as maintenance treatment for patients with ulcerative colitis, apparently over many years.¹ It cannot be tolerated by 10-15% of patients,² however, and many of its side effects can be attributed to its sulphapyridine content.^{3,4} Considerable evidence exists suggesting that for treating mildly active disease 5-aminosalicylic acid is the active substance.⁵⁻⁷ Olsalazine (Dipentum; azodisalicylate) consists of two molecules of 5-aminosalicylic acid linked with an azo bond. It has pharmacokinetic

properties similar to those of sulphasalazine,⁸ and when it is given orally high concentrations of 5-aminosalicylic acid are found in faecal water.⁹ Preliminary observations in patients with ulcerative colitis suggested that when given as a retention enema it was effective in treating active disease.¹⁰

We report two trials of olsalazine in patients with active ulcerative colitis. The first compared olsalazine given as an enema with a placebo preparation. The second compared oral olsalazine with placebo capsules.

Patients and methods

ENEMA TRIAL

Sixty patients (34 men, 26 women) with a mild attack of ulcerative colitis (defined according to the criteria of Truelove and Witts¹¹) entered the study. All patients had left sided disease, as determined radiographically. Table I lists the details of the patients, including the duration of disease and the number of patients taking sulphasalazine on entry to the study. Those who entered the study during a relapse and who were already receiving sulphasalazine continued to take this drug in the same dosage throughout the trial. Patients who were receiving corticosteroids (systemically or topically) or immunosuppressive drugs were excluded. Patients were randomly allocated (randomisation being restricted in blocks of four) to receive either an enema containing olsalazine or a placebo enema nightly for two weeks. The active enema contained 2 g olsalazine, 0.1 g methyl hydroxybenzoate, and 0.03 g propyl hydroxybenzoate in distilled water to 100 ml, and the placebo enema contained 0.001 g erythrosine, 0.025 g riboflavine, 0.1 g methyl hydroxybenzoate, and 0.03 g propyl hydroxybenzoate in distilled water to 100 ml; both enemas looked identical and were dispensed by the hospital pharmacist. Both active and placebo enemas were contained in yellow plastic bottles equipped with a nozzle set and a one way valve.

The study was approved by the hospital ethical committee, and informed consent was obtained from each patient.

Patients were assessed on entry to the study and after the two week trial. The number and consistency of stools and the presence of blood, mucus, and abdominal pain were recorded. Improvement in any of these symptoms was judged to represent a positive response. Any patient whose clinical state deteriorated during the trial was regarded as a failure and withdrawn from the trial. Sigmoidoscopy with rectal biopsy was performed on entry and after two weeks. Sigmoidoscopic and histological appearances were graded as described by Dick *et al* and Truelove and Richards, respectively.^{12,13} The pathologist did not know which treatment each patient was receiving.

Complete histological data were available for only 25 of the patients in the group given active treatment and 26 of those given placebo treatment who completed the trial. Blood was taken for routine haematological and biochemical analysis.

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ORAL TRIAL

Forty patients entered the trial of oral treatment (table I). Criteria for admission, the design of the trial, and assessment were the same as in the enema trial. Patients who were taking oral sulphasalazine stopped doing so on entry to the trial.

Patients received either 0.5 g olsalazine or one placebo capsule four times a day. Each active capsule contained 250 mg olsalazine and each placebo capsule 248.15 mg potato starch, 1.75 mg riboflavine, and 0.1 mg indigo carmine. The substances were packed into yellow gelatin snap fit capsules.

STATISTICAL ANALYSIS

Both trials were analysed as 2×3 contingency tables using a χ^2 test.

Results

ENEMA TRIAL

Table I shows that both groups were evenly matched for age, sex, duration of history, and previous treatment with sulphasalazine. Two patients, both receiving placebo enemas, failed to present for the second visit, and one patient was withdrawn because of rectal pain induced by the olsalazine enema.

TABLE I—Details of patients

	Enema trial		Capsule trial	
	Patients receiving olsalazine (n=30)	Patients receiving placebo (n=30)	Patients receiving olsalazine (n=20)	Patients receiving placebo (n=20)
No of men	19	15	12	6
No of women	11	15	8	14
Mean age (range) (years)	42 (18-75)	43 (19-72)	42 (19-67)	50 (15-81)
No of patients suffering first attack of ulcerative colitis	3	5	4	3
No of patients suffering relapse	27	25	16	17
Mean duration of history (years) (range)	8.4 (6 weeks-18 yrs)	8.8 (3 weeks-35 yrs)	6.9 (4 weeks-21 yrs)	8.1 (6 weeks-16 yrs)
No of patients already taking sulphasalazine	20	22	13	12

Table II shows the clinical and sigmoidoscopic results. Nineteen of the 29 patients receiving olsalazine enemas improved clinically, and 17 of these improved sigmoidoscopically. These responses were not significantly different from those seen in the 28 patients receiving the placebo enema, of whom 12 improved clinically and 11 sigmoidoscopically. Similarly, there was no significant difference in histological responses between the two groups, with 10 of 25 patients receiving olsalazine showing improvement compared with seven of 26 receiving placebo. Three patients in each group showed increased inflammation on histological examination, although their clinical and sigmoidoscopic appearances did not deteriorate.

The clinical, sigmoidoscopic, and histological responses in patients taking oral sulphasalazine were analysed separately. No differences were observed in the response to olsalazine between those patients who were receiving oral sulphasalazine at entry to the trial and those who were not. Five patients receiving placebo and three receiving olsalazine enemas were suffering their

TABLE II—Responses to olsalazine and placebo enemas

	Olsalazine enema (n=29)	Placebo enema (n=28)	Total (n=57)
Clinical response:			
Improved	19	12	31
Unchanged	9	14	23
Worse	1	2	3
Sigmoidoscopic response:			
Improved	17	11	28
Unchanged	11	15	26
Worse	1	2	3

For clinical response $\chi^2=2.98$, NS.

For sigmoidoscopic response $\chi^2=2.217$, NS.

first attack of ulcerative colitis. These numbers were too small for analysis, but the responses of these patients were similar to the overall results.

Apart from the rectal pain in one patient, no adverse reactions to olsalazine enemas occurred. There were no changes in blood count, results of liver function tests, or concentrations of electrolytes, urea, and creatinine that could have been attributed to the drug.

ORAL TRIAL

The two groups were reasonably matched (table I). No patients dropped out, and all were available for analysis. Complete histological data were not available for one patient in the group receiving olsalazine and two in the group receiving placebo.

Patients receiving oral olsalazine had a significantly better response ($p<0.02$) than patients treated with placebo capsules (table III). Thirteen of the 20 patients receiving oral olsalazine improved compared with eight of the 20 receiving placebo; but nine patients receiving placebo deteriorated compared with only one receiving olsalazine. Table III shows that in terms of sigmoidoscopic response the group receiving olsalazine fared better than the group receiving placebo ($p<0.05$). Only three patients in the group receiving olsalazine and one in the group receiving placebo showed histological improvement.

No differences were seen in patients who had not been treated before compared with those who had relapsed while taking sulphasalazine. Six patients entered the trial during their first attack: three received olsalazine

TABLE III—Responses to oral olsalazine and placebo capsules

	Group receiving olsalazine (n=20)	Group receiving placebo (n=20)	Total (n=40)
Clinical response:			
Improved	13	8	21
Unchanged	6	3	9
Worse	1	9	10
Sigmoidoscopic response:			
Improved	9	7	16
Unchanged	10	5	15
Worse	1	7	8

For clinical response $\chi^2=8.56$, $p<0.02$.

For sigmoidoscopic response $\chi^2=6.39$, $p<0.05$.

and three placebo capsules. Analysis of such small numbers contributes little, but their responses were similar.

Two patients taking olsalazine complained of mild headache and one of lightheadedness. Two patients had increased diarrhoea; in one this was associated with more active disease, but the other showed no deterioration in sigmoidoscopic or histological appearances. One of the patients receiving placebo capsules complained of nausea, but there were no other adverse reactions. No haematological or biochemical changes that might have been caused by olsalazine occurred.

Discussion

We found that patients with mild distal ulcerative colitis responded significantly better to oral olsalazine than to placebo

capsules. Although the proportion of patients receiving oral olsalazine (2 g daily) who had a good clinical response was greater than the proportion receiving placebo who did so, the most striking difference between the two groups was the clinical deterioration seen in those receiving the placebo. Greater clinical benefit might therefore be seen with longer periods of treatment or higher doses of olsalazine.

In both trials the response of those receiving placebo was high, of the order of 40%.⁵ Some studies have yielded similarly high rates of response to placebo,¹²⁻¹⁶ although others have reported rates of 20-30%.^{6, 17}

The failure to obtain a significant response to olsalazine enemas was surprising. Enemas of *N*-acetyl 5-aminosalicylic acid or 4-aminosalicylic acid, given according to a similar protocol, have resulted in significant rates of response.^{14, 17} It is conceivable that olsalazine was not adequately split to deliver two molecules of 5-aminosalicylic acid when administered as an enema. No data are available on this point, but as all patients in this trial were able to retain the enema this seems an unlikely explanation.

Sulphasalazine itself is not a powerful drug for the treatment of active ulcerative colitis and is considerably less effective than corticosteroids.¹⁸ Its principal use is in maintaining remission, and it is for this that olsalazine has been developed. Trials comparing olsalazine with sulphasalazine in the long term are now in progress.

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Possible mechanism for mianserin induced neutropenia associated with saturable elimination kinetics

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Abstract

Two cases of mianserin induced neutropenia associated with prolonged elimination of the drug were studied. In each case the pharmacokinetic profile suggested saturable elimination kinetics, and the temporal relation of mianserin concentrations and the neutrophil count suggested a direct toxic effect of mianserin on the bone marrow.

Until further studies are carried out the plasma mianserin concentration and neutrophil count should be measured in any patient who develops an infection while taking this drug.

Introduction

Mianserin is a tetracyclic antidepressant which has occasionally caused severe blood dyscrasias.¹ Pharmacokinetic studies of the drug in 14 elderly patients showed a terminal elimination half life of 27.0 (SD 13.1) hours, while in eight healthy adults it was 9.6 (1.9) hours.² Saturable elimination kinetics—as seen, for example, with phenytoin—has been said not to occur with mianserin.³ We report two cases of mianserin induced neutropenia associated with prolonged elimination of the plasma concentrations, which declined in a manner suggesting that the metabolising enzymes were saturated.

Case 1

A 60 year old woman was found to be neutropenic ($0.034 \times 10^9/l$; normal range $2.0-8.0 \times 10^9/l$) when she presented with a febrile illness due to right otitis externa. She had been prescribed mianserin 30 mg daily six weeks before instead of her usual amitriptyline. Other medications included labetalol 100 mg twice daily and hydrochlorothiazide 50 mg and amiloride 5 mg daily. Liver function values were mildly abnormal.

The plasma mianserin concentration was high initially and declined only slowly when the drug was withdrawn. This is shown in the figure along with the serial neutrophil counts. The initial slope of the mianserin elimination curve showed a half life of about 6.5 days. The terminal elimination half life was roughly 23 hours.

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