CLINICAL RESEARCH

Sulphasalazine retention enemas in ulcerative colitis: a double-blind trial

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Abstract

Thirty-four patients with ulcerative colitis completed a double-blind assessment comparing the efficacy of two weeks of treatment with nightly retention enemas containing 3 g sulphasalazine or placebo. Symptom grading, sigmoidoscopic appearance, rectal biopsy specimens, and diary records were used to assess benefit and side effects. The active drug conferred significant benefit compared with placebo as shown by several criteria, but this benefit was confined to patients not already taking sulphasalazine by mouth. Overall assessment showed improvement in 11 of the 16 patients (70%) given the active treatment but in only two of the 18 (11%) given placebo. No side effects attributable to the drug were observed, even in patients previously intolerant to oral preparations.

The logical therapeutic role of sulphasalazine enemas in ulcerative colitis would appear to be in patients who experience side effects such as nausea, abdominal discomfort, or headaches when taking the drug by mouth.

Introduction

Oral sulphasalazine is of proved value in the treatment of acute ulcerative colitis[1] and prevention of relapse,[2] but in up to 20% of patients side effects, particularly nausea, abdominal discomfort, and headaches, preclude its use.[3] Three studies[4-6] have claimed to show sigmoidoscopic and histological improvement in patients treated with sulphasalazine retention enemas. We report a further double-blind clinical trial of sulphasalazine retention enemas in 40 patients with ulcerative colitis in which we used both histological and clinical criteria to assess the effects of two weeks of treatment.

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Patients and methods

Patients were admitted to the study if they had sigmoidoscopically and histologically active ulcerative proctitis or colitis, were receiving neither systemic nor local corticosteroids, and were thought to be reliable witnesses. The study, which was approved by the Sheffield Area Health Authority (Teaching) (southern district) ethical committee, was conducted on outpatients, each of whom gave informed consent.

Assessment was double blind and was made before and after two weeks of treatment. At each assessment patients underwent sigmoidoscopy and rectal biopsy and blood was taken for estimation of haemoglobin concentration, white cell count, and erythrocyte sedimentation rate. Symptoms of general wellbeing, anorexia, and pain were assessed subjectively. Sigmoidoscopic appearances were classified as minimal or no bleeding, moderate bleeding, or considerable bleeding.

Patients received, on a randomised double-blind basis, either sulphasalazine enemas (Pharmacia (Great Britain) Limited) or a placebo preparation of similar colour and appearance and were instructed to retain each enema overnight. The treatment comprised sulphasalazine 3 g, sodium chloride 0·9 g, methylhydroxybenzoate 0·18 g, propylhydroxybenzoate 0·05 g, ethanol 0·6 g, and water to 100 ml; the placebo comprised talc 2·8 g, Tween 0·072 g, riboflavine 0·2 g, sodium chloride 0·9 g, methylhydroxybenzoate 0·18 g, propylhydroxybenzoate 0·05 g, and water to 100 ml. The patients were given diaries in which daily stool frequency, the consistency and presence of blood in each stool, and possible side effects were noted. At the end of the period both patient and observer stated whether they thought deterioration, improvement, or no change had occurred and specific inquiry was made about side effects.

Rectal biopsy specimens were fixed in 10% formol saline and processed routinely to give sections stained in haematoxylin and eosin. These were examined blind by one observer (JRG) using a protocol derived from that of Wright and Truelove,[7] and the degree of inflammation was classified as severe, moderate, mild, or absent. The accuracy of reporting was confirmed by re-examination later of all specimens and also by reporting of a random selection of specimens by an independent consultant pathologist.

Biopsy specimens taken at the beginning and end of the trial were compared and histological change determined. A scoring system was

used in which a change of one grade constituted one point, which was positive for improvement and negative for deterioration. A similar system was applied to change in symptoms and sigmoidoscopic appearances: 2 was much better, 1 improved, 0 no change, and −1 worse. The significance of histological, sigmoidoscopic, and clinical changes was then determined using the χ^2 test (with Yates's correction when applicable).

Diary information was used to determine mean daily stool frequency, the percentage of stools that were solid, and the proportion of bloody stools during a three-day control period before the start of treatment and during the last three days of treatment. The significance of these changes was determined using the paired *t* test.

Results

The treated group comprised 16 patients and the placebo group 18, withdrawals being due to non-compliance (one patient in the treated group) and failure to obtain repeat biopsy material. Disease severity at the beginning of the trial was similar in both groups, when the initial symptoms, sigmoidoscopic appearances, histological grading, and diary information were compared (table I).

Results were expressed separately for the 11 patients (four in the treated group and seven controls) who were taking oral sulphasalazine at the start of the trial. In these few patients the stable pretrial dose was maintained throughout the trial.

TABLE I—*Severity of disease at beginning of trial*

	Treated patients	Controls
Total No of patients	16	18
No with only distal disease	12	17
No taking oral sulphasalazine	4	7
Symptom severity:		
Mild	8	10
Moderate	8	6
Severe		2
Sigmoidoscopic activity:		
Mild	7	6
Moderate	9	7
Severe		5
Histological grade:		
Mild	4	6
Moderate	10	5
Severe	2	7
Mean (and SD) daily stool frequency	2·7 (1·0)	2·3 (1·2)
Percentage solid stool	31·3	35
Percentage bloody stool	85	48

Table II shows the change in disease severity in those subjects who were not taking oral sulphasalazine. Symptoms and sigmoidoscopic appearances improved greatly in the patients taking the active preparation, as shown by the scores of +16 for both. By contrast, the scores in the placebo group were only +3 (significance of difference between groups $p < 0.05$, χ^2 test with Yates's modification). In addition, more solid and less bloody stool was passed in the active group at the end of the trial ($p < 0.05$, paired *t* test), while in the placebo group no such difference occurred. The net changes in consistency and bloody stool in the active and placebo groups were compared: this difference also attained significance ($p < 0.05$, Wilcoxon rank test).

TABLE II—*Change in disease during trial in patients not taking oral sulphasalazine*

	Active treatment	Placebo
Total No of patients	12	11
No with only distal disease	9	11
Total symptom change score	+16*	+3
Total sigmoidoscopic change score	+16*	+3
Total biopsy change score	+8	−1
Mean (and SD) stool frequency:		
Beginning of trial	2·1 (1·1)	2·9 (1·6)
End of trial	2·1 (1·1)	2·9 (1·6)
Mean (and SD) % of solid stools:		
Beginning of trial	41 (33)	41 (36)
End of trial	70 (32)†	45 (33)
Mean (and SD) % of bloody stools:		
Beginning of trial	54 (41)	53 (40)
End of trial	23 (31)†	48 (45)

*Significance of difference between active and placebo treatment: $p < 0.05$.
†Significance of difference between values before and after treatment: $p < 0.05$.

The total change in histological grading was +8 in the active group compared with −1 in the controls; though this difference was not significant, it was derived from the observation that histological appearances improved in seven of the treated patients compared with two of the controls. In neither group was there a significant change in stool frequency or haematology, and side effects were equally common in both groups (eight and six complaints of lower abdominal discomfort associated with the enemas in the treated and control groups respectively). One patient in the placebo group experienced headaches, but nobody experienced any of the side effects commonly associated with sulphasalazine. Two patients in the treated group had previously experienced sulphasalazine sensitivity manifest as fever and rashes. Both tolerated the enemas without complication.

Four of the treated and seven of the control group continued oral maintenance sulphasalazine during the study. Table III shows the results in this group. No significant or consistent change occurred in either the treated or the placebo group, though the numbers concerned are clearly small.

TABLE III—*Change in disease during trial in patients also taking oral sulphasalazine*

	Active treatment	Placebo
Total No of patients	4	7
No with only distal disease	3	6
Total symptom change score	+3	+5
Total sigmoidoscopic change score	+3	+7
Total biopsy change score	−2	−1
Mean (and SD) stool frequency:		
Beginning of trial	3·4 (0·4)	2·5 (0·9)
End of trial	2·9 (1·8)	2·4 (1·1)
Mean (and SD) % of solid stools:		
Beginning of trial	2 (4)	32 (44)
End of trial	10 (20)	50 (48)
Mean (and SD) % of bloody stools:		
Beginning of trial	48 (35)	56 (44)
End of trial	20 (31)	20 (42)

Finally, overall improvement was assessed in all 34 patients, this being defined as improvement in two of the following criteria: clinical assessment, sigmoidoscopic appearances, percentage of bloody stools, and histology. Of the 16 patients given active treatment, 11 had improved at the end of the trial and five remained unchanged or were worse; of the 18 patients given placebo, two had improved and 16 remained unchanged or were worse. This difference between the two groups was significant ($p < 0.01$, $\chi^2 = 9.6$ with Yates's modification).

Discussion

We have shown unequivocal therapeutic efficacy of daily sulphasalazine enemas after only two weeks of treatment. None of the usual side effects associated with oral sulphasalazine developed, even in patients with a history of sensitivity. This is surprising since considerable amounts of total and component drugs are absorbed from the rectum.[8] Rectal sulphasalazine was effective in both severe and mild disease. Rather surprisingly improvement occurred in two of the three patients with extensive colonic disease who received the active treatment but were not taking oral sulphasalazine, so that benefit was not confined to the patients with distal disease.

The scoring system used in this study permitted a wider and more definitive analysis of the data obtained from clinical, histological, and diary information than was possible in other studies,[5 6] in which only the overall impression of improvement or deterioration was stated. Nevertheless, when our results were analysed in such a manner the overall incidence of improvement was 69% (11/16), which is similar to that found in previous studies of sulphasalazine enemas in ulcerative colitis[4–6] and of sulphasalazine suppositories in idiopathic proctitis.[9 10] This incidence of improvement is comparable with that observed in mild to moderate ulcerative colitis after oral sulphasalazine[1] and is consistent with the current hypothesis that the drug acts within the colon.

When sulphasalazine is administered by mouth most of it reaches the colon and is there almost completely split by colonic bacteria into sulphapyridine and 5-aminosalicylic acid.[8] The finding that suppositories of 5-aminosalicylic acid are effective in idiopathic proctitis[10] suggests that this is the active metabolite rather than the parent drug itself. This was also claimed by Khan *et al*,[4] but in their study 54 of their 62 patients were receiving oral maintenance treatment throughout the trial; unlike Khan *et al* we could not show any benefit of sulphasalazine enemas in these circumstances. Lack of additional therapeutic effect in patients already taking oral sulphasalazine is supported by the trial of Frühmorgen and Demling,[6] in which similar success rates were achieved in two studies, one of enema treatment alone and the other of combined administration of the drug, 3 g daily by mouth and 3 g daily by enema.

The logical therapeutic role of sulphasalazine enemas in ulcerative colitis would therefore appear to be in patients who get side effects such as nausea, abdominal discomfort, or headaches when taking the drug by mouth. In patients who are intolerant to sulphasalazine and experience frequent and rapid relapse on withdrawal of oral or local corticosteroids we have found that maintenance treatment with sulphasalazine enemas is useful and acceptable. Although sulphasalazine enemas also appear to be tolerated by at least some patients who develop rashes or fever when taking the oral preparation, it is more logical to desensitise such patients so that oral maintenance treatment may be continued.[11]

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(*Accepted 30 March 1981*)

ONE HUNDRED YEARS AGO The London College of Surgeons appears now to have determined upon a step, into which it would not be right to inquire too curiously as to the motives, but which is on the face of it for the public good, while by those who look below the surface it will, we believe, be seen to have an exactly opposite effect. The College proposes to increase and extend its medical examinations, with the ostensible view of remedying the present anomalous state of things, which allows a member of the College of Surgeons to go on the *Register* and to practice both medicine and surgery with impunity as a registered medical man. There can be no doubt of the anomaly, and, indeed, it is one which we first dwelt upon, and in respect to which for a short series of years we published numerical lists indicating the extent of the anomaly and the danger; but we by no means admit that this is the right way of remedying it, nor can we accept the view that in this case a defective remedy is better than none at all. That no one should be registered as a medical man who has not been tested thoroughly in medicine and midwifery as well as in surgery, in now a truism; but it is far from being equally apparent that it is therefore right that the College of Surgeons—a purely surgical body, whose examinations have only a surgical value, and have no other legal *status*—shall assume to itself the power, the duty, and the responsibility of becoming an examining body in surgery, medicine, and obstetrics. It is certain that, outside of surgery, the College of Surgeons, ruled by a body of pure hospital surgeons, will always be the worst examining body in the kingdom, just as in surgery it will always remain the best; and the marriage of defective examinations in medicine and obstetrics to complete examination in surgery is not what is required to bring about a sound state of medical education and registration. Any patching-up of this sort may be in the interest of the College, by giving an aspect of completeness to its diplomas, which no doubt the Council are right to consider; but it certainly is not in the interest either of medical education or of medical examination. It is not fair to students that they should be called upon in this way to go through multiple examinations by medic bodies in surgery and medicine, and by surgical bodies in medicine and surgery before they can acquire a qualification to practise. Nor is it right to the public that the College of Surgeons should set up an inferior standard in one set of subjects, in order to justify and enhance its power and position of examining in others. It is equally mischievous, as impeding the prospects of early and complete remedial measures in dealing with medical education and registration. It is much better fairly to face a difficulty, and openly to avow it, and to call for a remedy, than it is to apply a very imperfect measure, which is in itself an evil rather than a good. If the Council of the College of Surgeons were to go boldly and honestly to the Lord-President of the Privy Council, and inform him that they were in a difficulty as to their examinations—because their surgical examinations gives a right of registration, and therefore to practice—and to urge upon the Privy Council the necessity of taking steps to relieve them of that difficulty; and if, meantime, they were to combine with medical bodies, such as the College of Physicians, to give a conjoint degree, and not to give their own diploma under any other circumstances, they might claim to be acting in the public interest; and there is no doubt that their action would have a beneficial influence in determining early legislation. Their present step we regard as retrogressive and selfish: although, possibly, the application of such a description may surprise those who are the authors of it, and whose intentions may fairly be considered to be of quite an opposite kind. It is necessary, however, to look beyond the interest of corporations in this matter; and it is precisely because each corporation is still at the present moment fighting for its own hand, and working for its own interest in the name of the profession, that we once more earnestly protest against the present impotency of the Medical Council to regulate the actions of the corporations, and against the present absolute deadlock, brought about by those who object to the representation, in the Medical Council, of the profession, whose interests are outside and above those of the corporations. (*British Medical Journal*, 1881.)

ONE HUNDRED YEARS AGO Our Brighton correspondent writes to us: The fining of some obscure but noisy individuals for neglect of vaccination, and the selling of some furniture under a distraint warrant, has been made the excuse for rioting, and a somewhat serious assault on the vaccination officer, and on Dr Harris Ross, a well-known and esteemed surgeon in extensive practice, who holds an appointment as public vaccinator. Not content with orations about murder and blood-poisoning, black flags, brass bands, the Dead March in *Saul*, groans, and similar cheerful confessions of the faith that is in them, a large crowd gathered about the vaccinating station in High Street last week, very roughly handled Dr Ross as he left his carriage—hustled him, tried to throw him down, knocked his hat over his eyes, spat in his face, and, spite of two policemen, bruised him "till the breath almost left his body." It is needless to say that the sympathies of all respectable men are entirely with Dr Ross in this gross and unprovoked outrage, and we are glad to learn that he suffered no permanent injury. Summonses against four of the crowd were heard on Monday at the Brighton Town Hall. Three of them were fined, and the worst offender was sent for trial at the Quarter Sessions. (*British Medical Journal*, 1881.)