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Sulphasalazine in asymptomatic Crohn's disease

A multicentre trial[1]

SUMMARY During a six year period 43 patients with Crohn's disease were included in a double-blind controlled trial of sulphasalazine given for one year as a possible treatment for reducing the relapse rate after resection or in asymptomatic patients with established disease. No trend in favour of sulphasalazine over the control group was observed. The difficulties of such a trial due to the small number of patients entered from nine hospitals, the varied nature of the disease, and the high incidence of complications, such as intraperitoneal abscess formation, are discussed.

Patients with Crohn's disease treated by resection and asymptomatic patients with apparently quiescent disease are liable to recurrence of inflammation and symptoms. Sulphasalazine has been shown to reduce the relapse rate in ulcerative colitis (Misiewicz *et al.*, 1965; Dissanayake and Truelove, 1973) but to date there has been no comparable study in Crohn's disease. This double-blind trial was therefore designed to test whether or not sulphasalazine when given for one year would have a similar beneficial effect in patients with Crohn's disease. When the trial was planned there was no evidence that any treatment reduces the relapse rate so the effect of sulphasalazine has been compared with a control tablet.

Design of trial

PATIENTS INCLUDED

Patients with Crohn's disease treated by resection of diseased intestine in whom the diagnosis was confirmed by macroscopic and microscopic examination of the operation specimen were included within six months of the operation. Patients treated without resection, diagnosed radiologically or at laparotomy, were included if they were symptom-free but had had symptoms during the previous year; histological confirmation of the diagnosis was regarded as desirable but not essential in this group.

The patients were subdivided into four groups:

Resection	Group A	Excision of disease apparently complete.
	Group B	Macroscopic evidence of disease elsewhere in the gut at the end of the operation.
	Group C	No macroscopic evidence of residual disease but microscopic evidence of inflammation was present at the proximal and/or distal limit of excision.
No resection	Group D	

PATIENTS EXCLUDED

Patients were excluded if they were known to be sensitive to sulphonamides, aspirin, or sulphasalazine or had received a corticosteroid or immunosuppressive drug during the previous month.

EXPLANATION TO PATIENTS

It was explained to each patient that inflammation could recur and they were asked if they would be willing to take part in the assessment of a treatment which might reduce the possibility of further trouble.

NATURE AND ALLOCATION OF TREATMENT

After entry to the trial patients were allocated by a

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prearranged random scheme to a group taking sulphasalazine (99% pure in a film, non-enteric coating), 1 g three times daily, or to a group taking inert tablets with an identical coating. Side-effects were recorded only if complained of spontaneously and, in this event, the dose of tablets could be halved at the discretion of the clinician.

ASSESSMENT OF RESULTS

Patients were seen every two months or more frequently if symptoms developed. Details of symptoms and results of laboratory tests were recorded on a special form. Recurrence was defined as the development of symptoms and objective manifestations—for example, weight loss, fever, abdominal mass—attributable to Crohn's disease. In this event, the patient was withdrawn from the trial and the results regarded as a treatment failure. Barium follow-through or barium enema was performed when the patient completed one year in the trial without symptoms or sooner if there was recurrence.

WITHDRAWALS FROM TRIAL

Patients were withdrawn if they stopped taking the tablets because of side-effects, if clinical recurrence was diagnosed, or if a complication of the disease (see below) or other illness developed.

OTHER TREATMENT

Symptomatic treatments such as codeine phosphate, diphenoxylate or antispasmodics, and nutritional or mineral supplements were permitted during the trial.

Composition of treatment groups (Table 1)

During the years 1970-75 a total of 43 patients treated at nine hospitals were included in the trial, 22 of whom were allocated to the control group and 21 to the group given sulphasalazine. Little difference between the groups was found in respect to age or sex distribution, or the anatomical site of the Crohn's disease. Eleven of 22 patients in the control group had no anatomically demonstrable disease on entry to the trial, as compared with nine of 21 patients among those given sulphasalazine. One patient defaulted from the trial after the first attendance in each group, leaving 21 and 20 patients respectively available for analysis.

Table 1 *Clinical details of the two treatment groups*

	Control	*Sulphasalazine*
Total	22	21
Sex	12 M 10 F	8 M 13 F
Age (mean and range)	31·4 (13-57)	31·1 (18-58)
Distribution		
Small intestine	2	2
Ileocolic	18	16
Colonic	0	1
Recurrence at previous ileocolic anastomosis	2	2
Resection		
No residual disease detected	11	9
Residual macroscopic disease	1	4
Residual microscopic disease	8	2
No resection	2	6

Results (Table 2)

NO CLINICAL RELAPSE (22)

At the end of the year, 14 patients in the control group and eight in the sulphasalazine group remained well. The radiographic examination carried out at the end of the year in patients without clinical evidence of relapse showed evidence of recurrent disease in three patients in the control group and one in the sulphasalazine group. One of these patients in each group developed a clinical relapse during the year after the trial; the other two were well two and three years later. There was no clinical relapse during the year among any of the 15 patients who showed no evidence of residual disease after resection.

CLINICAL RELAPSE (six)

Details of the patients who relapsed are shown in Table 3. There were two relapses in the control group and four in the sulphasalazine group. This small difference may be explained by the presence of a greater number of patients treated without resection in the latter group.

COMPLICATION OF DISEASE (five)

There were five patients, one of whom died, who developed a definite or suspected intra-abdominal abscess. The following case reports describe three of these five patients to illustrate the problem:

Case 1 (M.24) Two year history, no medical treatment. Right hemicolectomy at which 40 cm of ileum and 60 cm of colon were removed. The resection specimen showed the typical pathological appearances of Crohn's disease and the two ends were free of disease. Symptom-free on entry to the trial and took sulphasalazine for nine days. Thereafter developed evidence of overwhelming infection and died three weeks later. Post-mortem examination showed peritonitis with extensive abscess formation, and abscesses in the liver, pancreas,and brain.

Case 2 (M.55) Nineteen month history, no medical treatment; known to have ankylosing spondylitis. Right hemicolectomy at which 50 cm of ileum and 12 cm of colon were removed. The proximal and distal limits of excision appeared free of disease. Took control tablets for six months,

Table 2 *Outcome in the two treatment groups: control (c) and sulphasalazine (s)*

	No clinical relapse		*Clinical relapse*		*Complications of disease*		*Withdrawn side-effects*	
	C	S	C	S	C	S	C	S
Resection								
Group A	10(2)	5(1)	0	0	1	2	0	2
Group B	0	1	1	0	0	0	0	1
Group C	3(1)	0	1	1	1	0	2	2
No resection								
Group D	1	2	0	3	1	0	0	1
Overall	14	8	2	4	3	2	2	6

Group A: no residual disease detected. Group B: residual macroscopic disease. Group C: residual microscopic disease. Figures in parentheses indicate patients with radiological evidence of recurrent disease.

Table 3 *Clinical details of patients whose disease relapsed*

Group	*Age, sex*	*Length of history (yr)*	*Clinical*	*Time in trial (months)*	*Evidence for relapse*
Control	M26	6	Resection of 110 cm jejunum + distal ileum + ascending colon	10	Vomiting, melaena, XR = duodenal Crohn's
Control	F47	9	Resection 48 cm mid-ileum. Bypass distal ileum	8	Pain, diarrhoea, Wt ↓ Hb ↓ Alb ↓
Sulphasalazine	M26	6	Resection 166 cm ileum + 77 cm colon for recurrent disease	10	Diarrhoea, anal abscess, arthritis, episcleritis. Recurrence on colonoscopy
Sulphasalazine	F21	8 m	Colonic disease proven by anal and rectal biopsy	2 w	Diarrhoea, pain, Hb ↓ ESR ↑
Sulphasalazine	F20	7 m	Terminal ileal disease proven by histology of appendix	6 (stopped treatment for 3 w due to pregnancy)	Vomiting, pain, diarrhoea. Laparotomy showed erythema and thickening of intestine
Sulphasalazine	M36	1	Extensive ileocolic disease	10	Pain, diarrhoea and bleeding. Wt ↓ Hb ↓ ESR ↑

then developed severe shoulder pain and, later, rigors. Found to have a chronic subphrenic abscess. *Case* 3 (M.24) Ten month history. Radiological diagnosis of Crohn's disease affecting the terminal ileum and right half of the colon, with an anal fistula. Minimal symptoms on entry to the trial. Took control tablets for four months but then developed an abscess in the right iliac fossa which was drained. Right hemicolectomy was performed 10 weeks later.

SIDE-EFFECTS, STOPPED TREATMENT (eight)
Two patients stopped taking control tablets during the first two months, one because of dyspepsia and the other because of nausea, diarrhoea, pruritus, and generalised pains. Of the six patients who stopped taking sulphasalazine, two complained of dyspepsia during the first week, three developed anorexia, nausea, or vomiting during the third or fourth months, and one developed a skin rash at eight months.

Discussion

This paper illustrates some of the difficulties in conducting controlled therapeutic trials in Crohn's disease. Despite the collaboration between nine hospitals, only 43 patients were included over five years and among these patients (two of whom defaulted) there was some heterogeneity as regards the anatomical extent of their disease. It was recognised at the outset of the trial that the relapse rate would be low and the rate observed (15%) during the year was of the order expected. A larger number of patients, a longer period of follow-up, or the selection of a high-risk group will be needed in future trials to detect a difference in relapse rate between two groups of patients who are asymptomatic at the start of the trial. It is noteworthy that no patient in this trial relapsed when there was no evidence of residual disease after resection and that, conversely, the relapse rate was high among patients in whom macroscopic or microscopic evidence of disease was present. It is difficult to persuade patients who are well to take a prophylactic treatment if they attribute any adverse effects to it and about one-fifth of the patients in this trial stopped taking the tablets because of side-effects. An unexpectedly high proportion (12%) of the patients in both groups developed an intraperitoneal abscess as a complication of the disease or its surgical treatment.

Despite these factors, there was no trend suggesting that sulphasalazine decreased the relapse rate among these patients, either after surgical treatment or among patients with quiescent disease. It seemed unlikely that continuation of the trial would give a positive answer and it was therefore stopped.

To date, six controlled trials of treatment in Crohn's disease have been reported (Rhodes *et al.*, 1971; Willoughby *et al.*, 1971; Rosenberg *et al.*, 1975; Anthonisen *et al.*, 1974; Klein *et al.*, 1974; Singleton, 1976). The total numbers in each trial were 15, 22, 20, 31, 27, and 234 patients respectively, emphasising the difficulty of studying a relatively homogeneous group of patients unless a large-scale collaborative trial is undertaken, as in the largest of these trials which was organised on a national basis and involved 14 centres. In that trial (Singleton, 1976) 48 patients with active symptomatic Crohn's disease were treated with sulphasalazine in a dose of 1 g/15 kg body weight per day for four months. The results were superior to those observed among 75 patients treated with control tablets for the same period ($P < 0.006$). Of the patients given sulphasalazine, 13 of 48 failed to complete the treatment period, in four cases because of side-effects. In another trial (Anthonisen *et al.*, 1974) sulphasalazine was shown to be of probable benefit among 17 patients with previously untreated Crohn's disease but no benefit was demonstrable among 14 patients with recurrent disease after surgical treatment. No trial has yet been reported of sulphasalazine as a maintenance treatment for patients with quiescent or surgically resected disease but results of such trials are awaited from Scandinavia and the United States.

The mode of action of sulphasalazine in inflammatory bowel disease is at present unknown but there is good evidence that the drug is split by bacterial action in the colon to yield its two constituents, sulphapyridine and 5-amino salicylic acid. Studies in man have shown that sulphapyridine and its metabolites are largely excreted in the urine, whereas 5-amino salicylic acid is present in high concentration in the faeces (Peppercorn and Goldman, 1973). It is possible that the efficacy of the drug shown by controlled trials in acute colitis (Baron *et al.*, 1962; Dick *et al.*, 1964), mainly of the distal type, and in colitis in remission (Misiewicz *et al.*, 1965; Dissanayake and Truelove, 1973) is due to the direct action of one or both of these metabolites on the colonic mucosa. If this is the case, the results in Crohn's disease could depend on the site of the inflammation, most of the patients in this trial having ileocolic disease, though there is at present no evidence on this point.

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