Clinical trial

Disodium cromoglycate in the treatment of ulcerative colitis and Crohn's disease

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SUMMARY A controlled clinical study on disodium cromoglycate (DSCG) at a dose of 800 mg per day versus placebo was carried out in 141 patients with ulcerative colitis and 25 patients with Crohn's disease. Those of the ulcerative colitis patients who had been on sulphasalazine treatment continued that treatment during the trial (101 patients). Forty patients were intolerant of sulphasalazine. No patient received steroids during the last month before the study. Patients with Crohn's disease had their possible sulphasalazine treatment stopped before the trial. No beneficial effect of DSCG as compared with placebo was found, as the DSCG and the placebo group showed the same number of relapses in patients with a clinically inactive ulcerative colitis at the start of trial and the same number of patients improving, deteriorating, and maintaining steady state in patients with clinically active ulcerative colitis at the start of trial. No synergy between DSCG and topically administered prednisolone could be demonstrated. There was no difference between relapse rate in DSCG and placebo groups in patients with Crohn's disease. No correlation between the eosinophil count in rectal mucosa and the outcome of the attack of ulcerative colitis could be demonstrated.

As disodium cromoglycate (DSCG) is of proven value in the treatment of bronchial asthma the early and preliminary observations of a similar effect in ulcerative colitis by Heatley *et al.*¹ and Mani *et al.*² were encouraging.

The findings in ulcerative colitis of increased histamine content in the colonic mucosa, particularly in patients with eosinophilia,³ further supported the possibility that DSCG, by its ability to stabilise the mast cells, would have a beneficial effect on patients with inflammatory bowel diseases or at least on some of the patients.

In view of these findings we decided in April 1977 to start a controlled double-blind study of DSCG versus placebo. The aims of the study were (1) to determine the effect on patients in an active stage of ulcerative colitis—that is, the *curative* effect—and (2) to determine its effect in preventing relapses in clinically inactive patients with ulcerative colitis and Crohn's disease—that is, the *prophylactic* effect.

During the trial period three other controlled studies were published,⁴⁻⁶ none of which gave evidence that DSCG was of therapeutic benefit in ulcerative colitis.

Methods

One hundred and forty-one patients with proven ulcerative colitis consecutively admitted during one year to our outpatient clinic gave their informed consent to taking part in the study. Eighty-one patients were clinically active and 60 patients clinically inactive. The study also included 25 patients with Crohn's disease in active or slightly active stages.

Criteria for exclusion from the trial were (1) need for steroid treatment and/or operation, (2) pregnancy or planned pregnancy in the treatment period, (3) known hepatic disorder or abnormal values for transaminase, bilirubin, or alkaline phosphatase in the blood, (4) other disease which could cause the patient's condition to deteriorate

during the trial period, and (5) a mental state which would make it difficult for the patient to cooperate.

DESIGN OF TRIAL

Each patient was randomly allocated to treatment with oral DSCG 800 mg per day (200 mg $\times$ 4) or identical placebo capsules containing dextran.

None of the patients had been on steroid therapy during the last month before the start of trial. One hundred and one ulcerative colitis patients had been on sulphasalazine treatment for more than one month (2–3 g per day) and continued that treatment during the trial. Forty patients were untreated, as they had previously experienced intolerance to sulphasalazine. The twenty-five patients with Crohn's disease had their sulphasalazine treatment stopped at entry into the DSCG trial, as sulphasalazine has not been proved to have the prophylactic effect in Crohn's disease that it has in ulcerative colitis.

The treatment period was one year or until additional treatment was needed. Once during this period prednisolone 25 mg per day for 12 days in the form of rectal enema was allowed without withdrawal from the trial in order to show a possible synergy between DSCG and local prednisolone.

The patients were seen routinely after one, three, six, nine and 12 months and at any time in between if a relapse occurred.

At each visit to the outpatient clinic the clinical and sigmoidoscopic activity was graded into inactive, slightly active, moderately active, and very active according to criteria given previously.⁷ A rectal biopsy specimen was obtained before entry to the study and examined histologically. The number of eosinophils per square millimetre of mucosal lamina propria was determined using an ocular grid as earlier described.⁸ Similarly, the number of mast cells in mucosal lamina propria and in the submucosal layer was estimated using toluidine blue staining.

Results

CURATIVE TRIAL

Eighty-one patients, 48 women and 33 men, with ulcerative colitis entered the study. Clinical data of the patient group are given in Table 1. All patients completed at least one month of treatment. Sixteen patients on DSCG and 13 on placebo showed continuously high or increasing activity which made it necessary to end the trial before one year, and to begin more active treatment. Two patients on DSCG and four patients on placebo were withdrawn from the trial because of side-effects, while personal reasons were given for ending the trial in one patient on DSCG and two on placebo. The number of patients improving clinically as well as sigmoidoscopically

during the trial is shown in Table 2. The figures for improvement in DSCG and placebo treated patients were very similar with no significant difference in favour of the DSCG treatment. Nor was there any difference between the DSCG and placebo groups when patients with and without sulphasalazine treatment were evaluated separately.

The eosinophil and mast cell counts in rectal biopsy specimens before the start of the trial are given in Fig. 1. No differences were found between patients improving and patients not improving

Table 1 Clinical data of 81 active ulcerative colitis patients

	DSCG n=40	Placebo n=41
Clinical activity		
Slight	15	13
Moderate	13	19
High	12	9
Sigmoidoscopic activity		
Inactive	8	5
Slight	8	9
Moderate	11	21
High	13	6
Length of DSCG treatment		
1 yr	21	22
<1 yr $\geq$ 1 month	19	19
<1 month	0	0
Sulphasalazine treatment		
—	12	11
+	28	30

Table 2 Number of patients showing improvement on DSCG and placebo treatment

	Improvement									
	Clinical				Sigmoidoscopic				Subjective after 1 month	
	After 1 month (no.) (%)	Total period (no.) (%)	After 1 month (no.) (%)	Total period (no.) (%)	After 1 month (no.) (%)	Total period (no.) (%)	After 1 month (no.) (%)	Total period (no.) (%)	(no.) (%)	(no.) (%)
DSCG n=40	19	48	13	33	13	33	9	23	17	43
Placebo n=41	22	54	16	39	11	27	14	34	12	29

Table 3 Clinical data of 60 inactive ulcerative colitis patients

	DSCG n=32	Placebo n=28
Duration of remission		
<8 weeks	4	4
$\geq$ 8 weeks <1 year	16	11
$\geq$ 1 year	12	13
Length of DSCG treatment		
1 year	22	23
$\geq$ 1 month <1 year	9	4
<1 month	1	1
Sulphasalazine treatment		
—	9	8
+	23	20

Fig. 1 Eosinophils and mast cells in rectal mucosa in ulcerative colitis patients with and without clinical improvement during trial with DSCG and placebo.

during the trial, and no differences were found between patients on DSCG and on placebo.

PROPHYLACTIC TRIAL

Sixty clinically inactive ulcerative colitis patients, 30 women and 30 men, entered the study. Forty-five completed the trial period, while 15 stopped treatment either because of relapse (five on DSCG and four on placebo) or because of side-effects (four on DSCG, none on placebo), or because of personal reasons (one on DSCG, one on placebo). The clinical data of the patient group are given in Table 3.

The total number of relapses during the trial period (Table 4) was higher in the DSCG group than in the placebo group, but the difference was not significant. As the expected effect of the drug was prophylactic—that is, relapse-preventing—no thera-

peutic effect of DSCG could thus be demonstrated. There was no difference between the DSCG and the placebo groups in the number of patients who were unaffected by additional steroid enema. This finding speaks against synergy between DSCG and prednisolone.

The rectal eosinophil and mast cell counts before the trial began in patients on DSCG and on placebo

Table 4 Results of treatment with DSCG and placebo in 60 patients with clinically inactive ulcerative colitis

	Number of patients			
	With relapse (no.)	(%)	Without relapse (no.)	(%)
DSCG n=32	12	37.5	20	62.5
Placebo n=28	6	21	22	79

Fig. 2 Eosinophils and mast cells in rectal mucosa in ulcerative colitis patients with and without relapse during prophylactic trial with placebo and DSCG.

with and without relapse, respectively, are shown in Fig. 2. No differences were found between the groups.

CROHN'S DISEASE TRIAL

Twenty-five patients, nine women and 16 men, with Crohn's disease entered the study. Clinical data on

Table 5 Clinical data of 25 patients with Crohn's disease

	DSCG n=11	Placebo n=14
Clinically		
Inactive	5	4
Slightly active	6	10
Sulphasalazine before trial		
+	6	5
÷	5	9
Affected part of GI tract		
Ileum only	6	3
Colon only	3	2
Ileum + colon	2	9
Length of treatment		
One year		3
≥1 month <1 year	6	10
<1 month	2	1

the patients are given in Table 5. Only three patients on DSCG and three patients on placebo completed the trial period. Fourteen patients were withdrawn because of relapse and five because of side-effects (three on DSCG and two on placebo).

Table 6 shows the number of patients with relapse in the DSCG and the placebo group, respectively. The relapse rate was high in both groups, 45 and 64%. The difference is not significant. The high relapse rate was possibly due to the simultaneous cessation of sulphasalazine treatment.

The eosinophil and mast cell counts are shown in Fig. 3 in patients on DSCG and on placebo as well

Table 6 Results of treatment with DSCG and placebo in 25 patients with Crohn's disease

	Number of patients			
	With relapse		Without relapse	
	(no.)	(%)	(no.)	(%)
DSCG n=11	5	45	6	55
Placebo n=14	9	64	5	36

Fig. 3 Eosinophils and mast cells in rectal mucosa in patients with Crohn's disease with and without relapse during prophylactic trial with DSCG and placebo.

as in patients later having a relapse and patients without relapse. No differences were found between the groups.

Discussion

Consistent with the lack of curative effect of DSCG shown in the present study, Buckell *et al.*⁴ found no benefit of DSCG in ulcerative colitis patients selected as resistant to medical treatment—that is, patients receiving the optimal medical treatment available and having DSCG or placebo added. Our patients belonged to the milder part of the disease spectrum, as they did not receive or need steroids at the start of the trial. These two studies then corroborate each other and show that patients with active ulcerative colitis are not helped by treatment with DSCG.

Our study could not confirm the findings by Heatley *et al.*¹ that the treatment might be effective in the subgroup of patients with a high eosinophil cell count in the colonic mucosa.

The ineffectiveness of DSCG in preventing relapse

that this study demonstrates is in agreement with the findings of Willoughby *et al.*⁵ who compared DSCG with sulphasalazine and with DSCG + sulphasalazine in a six month study. They demonstrated a very high relapse rate in patients on DSCG alone (54.1%) and lower and equal relapse rates in patients on sulphasalazine alone and sulphasalazine + DSCG. As we continued the sulphasalazine treatment in all patients who tolerated this drug we expected and found lower relapse rates in both groups. Only 17 of our patients were intolerant to sulphasalazine and therefore were treated only with DSCG or placebo. Of these patients four on DSCG and two on placebo experienced a relapse in the trial period.

Dronfield and Langman⁶ found the relapse rate in patients on sulphasalazine and on DSCG to be 30% and 71%, respectively, the latter percentage being similar to the relapse rate found in patients on placebo by Misiewicz *et al.*⁹

The recent findings by Heatley and James¹⁰ that a high eosinophil count in the colonic mucosa

predicts a favourable outcome of the attack of ulcerative colitis could not be confirmed in our study.

Only one controlled study on the effect of DSCG on Crohn's disease has been published before. Grundman *et al.*¹¹ found no difference between DSCG and placebo treatment in the activity index or for any symptom, sign, or laboratory result. In our study only three patients with Crohn's disease in the DSCG group and three in the placebo group completed the trial period. There was a high recurrence rate in both groups, possibly in part because sulphasalazine treatment was discontinued at the start of the trial. The results are not encouraging, not even when the low number of patients is considered.

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