

Disodium cromoglycate in the treatment of chronic proctitis

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SUMMARY The effect of topical disodium cromoglycate (DSCG) has been examined in 30 patients with chronic active proctitis using a double-blind crossover trial. Each treatment period was four weeks and patients were given DSCG 200 mg by enema twice daily and 100 mg orally three times each day. Twenty-six patients completed the trial successfully, 14 responded to DSCG treatment, two improved with placebo, and 10 responded to neither.

Patients who responded to DSCG had significantly more eosinophils in their rectal biopsies than those who failed to respond and in some instances the counts were very high. The findings support the hypothesis that an allergic reaction is important in the pathogenesis of proctitis.

Disodium cromoglycate (DSCG) is of proven clinical value in allergic bronchial asthma where it is thought to reduce the degranulation of mast cells in bronchial mucosa (Pepys, Hargreave, Chan, and McCarthy, 1968). Chronic proctitis is an inflammatory condition of unknown aetiology affecting the rectal mucosa. In a related condition, ulcerative proctocolitis, mast cell degranulation is a common feature in rectal biopsies (Bercovitz and Sommers, 1966). It is therefore pertinent to examine whether DSCG, if given topically, would have a beneficial effect in patients with proctitis. Proctitis is a particularly suitable condition to examine because in addition to recording any symptomatic response, the rectal mucosa can be both inspected and biopsied directly. A randomized, double-blind crossover trial was designed to examine the effect of this compound in a group of patients with chronic proctitis.

Methods

PATIENTS

Thirty patients with chronic proctitis were included in the trial but four were subsequently withdrawn. All had active symptoms which included rectal bleeding, the passage of mucus, and a change in bowel habit, usually with increased frequency. In all the rectal mucosa was abnormal on sigmoidoscopy. The subsequent details refer to the 26 patients

who completed the trial, nine of whom were male and 17 female patients. The mean age was 39 years (range 18 to 74 years). The duration of previous symptoms was between three and 120 months (mean 33 months); 20 of the patients had had symptoms for more than one year. The severity of symptoms during the first five days of the trial is given in fig 1; half of the patients had blood loss on most days with between two and four stools daily. Four patients continued with additional therapy, taking between 0.5 to 2 g of sulphasalazine throughout the trial. One of these patients also had a predsol enema each day and a further two patients received predsol enemas without sulphasalazine throughout the trial. All had a normal barium enema examination during the previous six months.

DESIGN OF TRIAL

Patients entered the trial in a randomized way and received treatment with DSCG and a placebo, each for a period of four weeks. Neither the clinician nor the patient was aware of which treatment was being given. In the first period, they received either DSCG or placebo and in the second period the alternative treatment. One hundred mg of DSCG was given in gelatine capsules three times daily by mouth and 200 mg was self administered as an enema, after first dissolving the DSCG in 40 ml of warm tap water. The placebo was glucose in identical capsules.

Patients were assessed at the commencement of the trial and then after four and eight weeks. On each

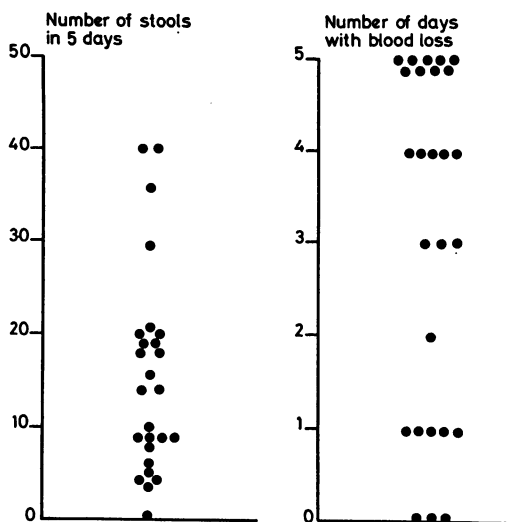


Fig 1 The severity of symptoms for each patient during the first five days is shown in the number of stools and the number of days on which blood loss occurred.

occasion sigmoidoscopic examination was carried out using a standard Lloyd-Davies instrument. A system of grades was used similar to that described by Baron, Connell, and Lennard-Jones (1964), for this has been shown to give little observer variation; grade I was normal mucosa, grade II hyperaemic mucosa with loss of the normal vascular pattern, in grade III there was bleeding on light contact or spontaneously, and in grade IV there were severe changes with an excess of mucus, pus, mucosal haemorrhages, and occasional ulceration. The severity was noted at varying distances from the anal margin, for the most severe change was commonly limited to the lower rectum. Each patient was followed by the same clinical observer during the trial. A rectal biopsy was taken at each sigmoidoscopic examination from a point on the anterior rectal wall about 8 cm from the anal margin.

During each four-week period patients recorded on a diary card the frequency of bowel motions each day and the occurrence of rectal bleeding. The records from the last 14 days of this four-week period were subsequently used for analysis; this effectively interposed two weeks between the assessment periods. In addition, at the end of each four-week period patients indicated their clinical progress by choosing one of the following words: excellent, good, fair, bad, or terrible; these were taken as an overall assessment by the patient and were used in subsequent analyses.

HISTOLOGY

Rectal biopsies were examined without knowledge of the patient or treatments given. The acute inflammatory reaction was graded as normal, moderate, or severe, using paraffin sections stained with haematoxylin and eosin. This was based on the degree of acute inflammatory infiltrate of the lamina propria, crypt abscesses if these were present, and early migration of polymorphs across the basement membrane of epithelial tubules. In addition, sections were stained with carbol chromatrobe which specifically stains eosinophil cells. Eosinophil counts were made over five high-power fields. A further section was stained with toluidine blue to stain mast cells. Twelve biopsies were taken from control patients who did not have inflammatory bowel disease; most of them had had a recent change in bowel habit. These biopsies were used for comparison and in none did the eosinophil count exceed 10 cells per five high-power fields.

Blood was taken to measure the erythrocyte sedimentation rate (Westergren), haemoglobin, total white cell count, absolute eosinophil count, and serum IgE (Johansson, Bennich, and Wide, 1968).

Results

The three measurements of clinical response were a change on sigmoidoscopic examination, details from the diary card of bowel frequency and blood

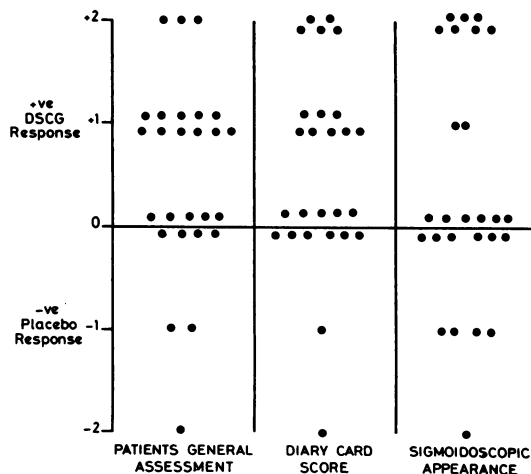


Fig 2 Change in the clinical severity of proctitis for each patient was based on the patient's assessment, the diary card record of stool frequency and blood loss, and the sigmoidoscopic appearance. The two treatment periods were compared and scored +1 or +2 for a favourable response to DSCG, and -1 or -2 for a placebo response.

with the DSCG period in nine and a relative decrease in four. The changes which occurred in 'non-responders' were variable; in three there was little change, in three there was a relative increase, and in two a relative decrease in the placebo period.

Nine of the 14 patients who responded to DSCG had either moderate or severe inflammatory changes in the rectal biopsies. Four of the 12 who did not respond also showed acute inflammatory changes, and, in a further patient who had severe proctitis, repeated attempts to obtain satisfactory biopsies were unsuccessful. There was a poor correlation between the mucosal inflammatory reaction and changes in the clinical response and sigmoidoscopic appearance.

The number of mast cells counted per five high-power fields ranged between 0 and 39; in 43 of 63 biopsies the count was less than three per five high-power field and showed no consistent change with clinical response.

Four patients were withdrawn from the trial because they either failed to cooperate or developed an unrelated illness; no side effects from DSCG were encountered.

Discussion

Disodium cromoglycate has a topical action on the bronchial mucosa and reduces the effect of inspired antigens in some patients with extrinsic asthma (Pepys, Hargreave, Chan, and McCarthy, 1968). The normal sequence of events is that the interaction of antigen and antibody causes mast cell damage (Orr, Pollard, Gwilliam, Jessie, and Cox, 1970). These cells then break down, releasing histamine, serotonin, and 5-hydroxytryptamine, which cause tissue damage. Disodium cromoglycate stabilizes the mast cells in bronchial mucosa and blocks these events. The only report of a related effect in the gastrointestinal tract is a beneficial response to DSCG in four infants with gastrointestinal protein intolerance (Freier and Berger, 1970). The pathogenesis of both proctitis and ulcerative colitis remains unknown and the possibility that an allergic component may play a significant role has frequently been suggested (Rider, Moeller, Devereaux, and Wright, 1960; Wright and Truelove, 1965). If there is such a component, then DSCG may be of value. Since the compound remains unchanged during its transit through the gastrointestinal tract and less than 2% is absorbed, oral administration may be effective in lesions of the lower gastrointestinal tract.

Before commencing the trial 14 patients with proctitis were treated for between two to eight weeks with 200 mg three times each day given orally, or

200 mg twice daily by enema, or a combination of the drug given orally and by enema. Ten patients appeared to show a beneficial response so that we were encouraged to proceed with a controlled trial.

The trial was double-blind and of crossover design which made it a sensitive indicator of any response. The patients showed a positive response to either DSCG, the placebo, or failed to respond to either treatment. Fourteen showed some response to DSCG, two to placebo, and 10 to neither of these. We are particularly concerned with the comparison between those patients who responded to, and those who failed to respond to disodium cromoglycate.

Although patients with ulcerative colitis respond to treatment with corticosteroids, only about 25% of patients with proctitis can be expected to go into full remission with topical treatment (Lennard-Jones, Baron, Connell, and Jones, 1962). Those with a long history of symptoms appear less likely to respond to this form of treatment (Truelove, 1959). Sulphasalazine may be of additional value in some patients, either by inducing or maintaining a clinical remission. However, because of a failure to respond to conventional treatment, or undesirable side effects in some patients, there is good reason to look for alternative forms of therapy. Compounds like DSCG may have a place in the future management of patients with proctitis.

Disodium cromoglycate acts at a particular point in the inflammatory reaction, and as half of our patients responded to this treatment, we may have identified a part of the inflammatory mechanism in patients with proctitis. In considering other related evidence which supports an allergic component in proctitis, one must consider the data collected from patients with ulcerative colitis. It would seem reasonable to do this because some cases of proctitis later spread to involve the proximal bowel and the condition is then indistinguishable from ulcerative colitis. Both the sigmoidoscopic appearances and the pathology of the two conditions are similar and many authors regard them as the same disease process (Goligher, 1953; Naish, 1953; Hill, 1957; Truelove, 1959; Lennard-Jones, Cooper, Newell, Wilson, and Jones, 1962). Histological changes in proctocolitis include an increase in the number of both chronic and acute inflammatory cells, with a marked increase in eosinophils in some patients; mast cells may also be present in excess and are frequently degranulated. This cellular increase is likely to be important in the pathogenesis of the disease, since during activity, both mast cells and eosinophils are greatly increased but fall to normal with remission (McAuley and Sommers, 1961; Hiatt and Katz, 1962; Bercovitz and Sommers, 1966; Wright and Truelove, 1966).

Allergic tissue reactions are frequently associated with an increased number of eosinophils (Litt, 1964). These are found in the bronchial mucosa associated with extrinsic asthma and the nasal mucosa in hay fever. Large numbers of eosinophils can sometimes be identified in the stools of infants with milk allergy (Rosenblum and Rosenblum, 1952). The rectal biopsies from our patients with proctitis showed a wide range in their eosinophil content; in only four of 21 patients, all of whom failed to respond to DSCG, were the counts in the normal range; in some instances the counts were very high (fig 4).

The association of proctocolitis with a peripheral blood eosinophilia has also been noted in some patients and this eosinophilia frequently disappears when the inflammatory disease goes into remission (Riisager, 1959; Riis and Anthonisen, 1963; Wright and Truelove, 1966). Thirteen of our patients had a peripheral eosinophil count greater than 200 per cmm and two greater than 400 per cmm; these are values which would be considered by some to be greater than normal.

The histamine content of tissue involved in an allergic reaction is sometimes considerably increased. The histamine content of rectal mucosa in patients with ulcerative colitis has been examined and is high during a clinical relapse, but falls to normal with clinical remission (Binder and Hvidberg, 1967). The concentration of histamine is proportional to the number of eosinophils present in the surface mucosal exudate. It is quite probable that the high histamine content and eosinophilia in rectal exudates reflect an allergic reaction in the mucosa. The allergic release of histamine from sensitized mast cells may follow an antigen-antibody reaction, and this in turn would be inhibited by disodium cromoglycate. It has even been suggested that the pathology of ulcerative colitis is due to release of histamine into the tissues (McGovern and Archer, 1957). This study provides evidence to suggest that immune mechanisms are important in the pathogenesis of some cases of proctitis and in addition DSCG or similar agents may have some part to play in the routine management of these patients.

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