

Clinical trial

Treatment of distal ulcerative colitis (proctosigmoiditis) in relapse: comparison of hydrocortisone enemas and rectal hydrocortisone foam

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SUMMARY Thirty patients with distal colitis (proctosigmoiditis) in relapse were randomly allocated to twice daily treatment with traditional aqueous hydrocortisone enemas (Cortenemas) or a suspension of hydrocortisone in an inert foam base (Colifoam). Each treatment contained the same amount of hydrocortisone. Clinical, sigmoidoscopic, and histological response was assessed after two weeks. Both agents were effective, and broadly similar in terms of objective improvement, but subjective improvement was greater with the foam preparation, and several patients expressed a preference for this mode of treatment.

Patients with ulcerative colitis confined to rectum and sigmoid colon have a good prognosis in terms of life expectation,¹ but suffer the same distressing symptoms of urgency and diarrhoea as those with more extensive colonic involvement.² The severity of symptoms is largely determined by the degree of rectal inflammation^{2,3} and corticosteroid enemas are often effective in inducing remission.⁴⁻⁶ Although systemic absorption of steroid from retention enemas containing both hydrocortisone^{7,8} and prednisolone-21-phosphate^{9,10} has been demonstrated, the consensus of opinion is that their efficacy in colitis is, at least in part, due to a local effect on the inflamed rectum.⁹⁻¹¹ Unfortunately, the traditional aqueous steroid enema is not well tolerated by all patients, and a proportion have considerable difficulty in retaining the preparation.¹² It has been claimed that this problem can be overcome by using a suspension of hydrocortisone in an inert foam base (Colifoam, Stafford-Miller Ltd), thus improving its acceptability to the patient without loss of efficacy.^{13,14} The foam carrier—but not necessarily the therapeutically active hydrocortisone—spreads retrogradely to the sigmoid colon or beyond in patients with active colitis,¹⁵ though less extensively than aqueous enemas,¹⁶ and both pre-

parations may be useful in treating patients with colitis extending proximally beyond the rectum. Despite its theoretical attractions, and widespread clinical use over the last decade, rectal hydrocortisone foam has not been subjected to any controlled trials. We have compared rectal hydrocortisone foam with a conventional steroid enema in the treatment of patients with distal colitis (proctosigmoiditis) in relapse.

Methods

PATIENTS

Thirty patients attending the Colitis Clinic at Leeds General Infirmary were studied during symptomatic and sigmoidoscopic exacerbations of distal colitis (proctosigmoiditis) defined as inflammation not extending proximally beyond the junction between sigmoid and descending colon. Disease extent was assessed by sigmoidoscopic and radiological evidence (double contrast barium enema), together with colonoscopy where available. Patients in whom there was doubt about the extent of disease, such as those with proctitis without an upper limit on sigmoidoscopy and a normal barium enema, were excluded from the study, as were those with a diagnosis or clinical suspicion of Crohn's disease. Patients currently or recently receiving therapy with any oral or rectal steroid preparation were

excluded from the study, but all other treatment including sulphasalazine was continued unchanged.

The clinical criterion for entry into the trial was symptomatic relapse, and patients with chronic continuous symptoms were not included. Symptoms leading to consideration for the study were diarrhoea with or without blood, urgency with or without precipitate incontinence, and tenesmus. Patients in symptomatic relapse so defined, who were known to have distal disease on the basis of recent investigation, were asked to participate in the trial after full explanation. Those agreeing were referred to one of us (RJD) who performed all the sigmoidoscopies. If sigmoidoscopic activity confirmed the clinical impression of relapse the patient was entered into the trial and a rectal biopsy taken from the inflamed area, the distance from the anus being noted. Sigmoidoscopic appearance was graded by a simple points system from 1–3 to indicate activity (Table). No attempt was made to achieve a more subtle grading of activity, as the use of less 'hard' criteria leads to considerable observer inconsistency.¹⁷ After sigmoidoscopy, the patient's symptoms were assessed in detail, he was returned to the referring physician (ATRA or WSJR), and was randomly allocated to two weeks' treatment with either conventional hydrocortisone enemas (prescribed as Cortenema, Bengue & Co, Ltd, which consists of a single dose plastic disposable container with lubricated nozzle for rectal insertion containing 100 mg hydrocortisone in 60 ml saline); or to treatment with hydrocortisone foam, by selection of unlabelled envelopes. The hydrocortisone foam (Colifoam, Stafford-Miller Ltd) was prescribed as a multi-dose pressurised cannister from which individual doses of 5 ml, containing 90–110 mg hydrocortisone were dispensed into a special plastic syringe for rectal insertion. Careful instructions were given to ensure optimal use of each preparation and patients were

instructed to use them on retiring and again in the morning, after they had opened their bowels. In the event of difficulty in retaining the preparation they were instructed to lie on their left side for at least 30 minutes after insertion, and if necessary raise the foot of the bed. They were asked to go about their normal tasks if possible after the morning treatment. Each patient was given a diary card to record daily bowel actions during the course of treatment. After two weeks the patient was reviewed, and a repeat sigmoidoscopy with grading of activity, and rectal biopsy at the same distance from the anus as previously, was performed by RJD without knowledge of treatment. The patient was then questioned about symptoms, noting the presence or absence of urgency and tenesmus, and the number of bowel actions per day. In addition the following questions were asked. (1) Did you find insertion of the preparation easy or difficult? (2) Did you find the preparation comfortable or uncomfortable? (3) Did you have difficulty retaining the morning treatment? (4) Has the treatment improved your symptoms? (5) Have you any other comments about the treatment?

HISTOLOGY

Biopsies were examined without knowledge of clinical data or treatment by a pathologist with a special interest and experience in inflammatory bowel disease (MFD). Multiple criteria were assessed on each biopsy, and those reported in this study referred to the degree of active inflammation. An 'active inflammation score' was derived for each biopsy by summing scores on an arbitrary scale of 0–3 for each of the following three characteristics: polymorph infiltration, mucus depletion, and superficial epithelial degeneration (Table). Thus a score of 0–9 was allocated to each biopsy. Many other features such as glandular distortion and oedema were, of course, recognised, but the above were selected as giving the best histological index of current activity.

Data were analysed using the chi-square test and Student's *t* test or Wilcoxon's rank sum test as appropriate for parametric or non-parametric data.

Results

Thirty patients were studied, 15 allocated to each treatment group. The groups were broadly similar in terms of age (enema group median age 46 years; range 22–63 years), (foam group median 39 years; range 22–56 years), sex (enema group, nine males; foam group, seven males), and extent of disease (confined to rectum, enema group, six, foam

Table *Methods of sigmoidoscopic and histological grading*

Sigmoidoscopy		Histology	
Appearance	Score	Feature	Score
Normal vascular pattern	0	Polymorph infiltration	0–3
Vascular pattern reduced or absent	1	Mucus depletion	0–3
Friability-bleeding to touch only	2	Superficial epithelial degeneration	0–3
Spontaneous bleeding	3	Total—'active inflammation score'	0–9

Note that the allocation of one sigmoidoscopic appearance excludes all others, whereas the 'active inflammation score' is the sum of the scores allocated for each histological feature.

group, eight—the remainder having sigmoid involvement).

EFFECT OF TREATMENT ON SYMPTOMS

Diarrhoea

There was a significant reduction in diarrhoea, measured as number of bowel actions per day, in both groups. Each group improved from a median of four bowel actions per day before treatment to two per day after treatment ($P < 0.05$ for both groups, Wilcoxon's signed rank test). In the enema group 10 patients showed a reduction in bowel actions per day, compared with 12 patients in the foam group and this difference in the proportion of patients showing improvement was not significant.

Urgency

Twelve patients in the enema group suffered from urgency of defaecation before treatment, and this symptom was abolished in eight (66%). Nine patients in the foam group suffered from urgency, which was relieved in seven (77%). There was no significant difference in the relief of urgency between the two treatments.

Tenesmus

Tenesmus was an initial symptom of 12 patients treated with corticosteroid enemas and was relieved in nine (75%), and was present in nine patients treated with the foam preparation and relieved in seven (77%). Again this did not represent a significant difference in response between the two treatment groups.

Patients' subjective improvement

At the end of the two week course all patients were asked if they considered that the treatment had improved their symptoms. Fourteen of the 15 patients treated with the foam reported subjective improvement (93%), whereas only nine patients (60%) treated with conventional enemas thought their symptoms had improved, a significant difference ($\chi^2 4.658$, $P < 0.05$) in favour of the foam preparation.

EFFECT OF TREATMENT ON SIGMOIDOSCOPIC APPEARANCE

The two groups were comparable in sigmoidoscopic grading before treatment, both having a median sigmoidoscopic activity score of two. In the enema group there were four patients with an activity score of one, nine with a score of two, and two with a score of three; in the foam group there were two patients with a score of one, nine with a score of two, and four with a score of three. In both treatment groups improvement was confirmed by a significant re-

duction in sigmoidoscopic activity score ($P < 0.01$ for both, Wilcoxon's signed rank test). In no case did the sigmoidoscopic appearance deteriorate, although there was no change in seven patients in the enema group, and six in the foam group. There was no significant difference between treatments in the number of patients showing sigmoidoscopic improvement—eight in the enema group, and nine in the foam group.

Histology

There was no significant difference between pre-treatment 'active inflammation score' in the two groups. In the enema group there was a significant improvement in active inflammation score from 4.4 ± 0.5 (mean \pm SEM) before treatment, to 2.5 ± 0.5 after treatment ($t = 2.536$, $P < 0.05$). In the foam group the initial active inflammation score was 5.2 ± 0.6 (mean \pm SEM) and this changed insignificantly after treatment to 4.9 ± 0.8 . However, this apparent superiority for enema treatment was not confirmed at an accepted level of significance when the two treatments were compared directly, as 10 patients treated with enemas showed histological improvement—namely, a reduction in active inflammation score—compared with seven patients treated with the foam ($\chi^2 = 1.2217$, P NS).

EASE OF INSERTION AND COMFORT

Only one patient in each group reported difficulty in insertion or discomfort in use.

DIFFICULTY IN RETAINING MORNING TREATMENT

All patients were encouraged to pursue their normal tasks after the morning medication. Eight patients in the enema group reported difficulty in retaining the treatment, whereas none of the 15 patients receiving the foam experienced any difficulty, and this difference is highly significant ($P < 0.001$). Of the eight patients in the enema group who had difficulty in retaining the treatment, four considered that this led to important impairment of their ability to carry out normal tasks. However, when the subgroup of enema patients experiencing difficulty with retention is compared with those undergoing the same treatment who experienced no such difficulty, no significant differences in response to treatment emerge in terms of diarrhoea, urgency, tenesmus, histology, sigmoidoscopic improvement, or the patient's own subjective improvement. Similarly, if the subgroup of patients experiencing difficulty retaining the enemas is compared with the total foam group (none of whom reported difficulty with retention), no significant differences emerge in terms of diarrhoea, tenesmus, sigmoidoscopy, or histology.

Although the foam group report a better subjective improvement than the enema subgroup experiencing difficulty with retention, this is merely a reflection of the significantly greater subjective improvement found in the foam group as a whole. Thus there is no evidence that difficulty in retaining the medication *per se*, leads to a less satisfactory response.

OTHER COMMENTS

The only other difference between the two treatment groups was in respect of additional comments from the patients after completing treatment. Twelve patients commented spontaneously that they had previously received the alternative treatment, and this statement was verified by referral to the hospital records. Of these 12 patients 11 expressed a preference for the foam, and one expressed a preference for the traditional enemas.

Discussion

The efficacy of rectal hydrocortisone in treating exacerbations of colitis was conclusively demonstrated by Truelove in 1958,⁴ and has been confirmed many times.⁵⁻⁷ Such compelling evidence precluded the use of a placebo group in the present study. The clinical and sigmoidoscopic remission rate in both our treatment groups approached the 70% reported by Truelove after a two week course of hydrocortisone given by rectal drip¹¹ and greatly exceeded the placebo remission rate.^{4,5} A similar remission rate has been shown with the same preparation (Cortenna) used in this study.⁷

There was little difference between the conventional enema and the foam preparation in terms of sigmoidoscopic appearance, which improved in 53% of the enema group and in 60% of the foam group. However, the histological grading of active inflammation improved significantly only in the enema group. An apparent discrepancy between histological and sigmoidoscopic improvement after rectal hydrocortisone has been noted before,¹⁸ but the lack of a significant improvement in 'active inflammation score' in the foam group is of doubtful importance in view of the fact that no significant differences emerged between the two treatments when compared directly in terms of the number achieving an overall histological improvement.

Important differences emerged between the two treatment groups when the patients' subjective assessment of overall symptomatic improvement was considered, but this was not apparent on the clinicians objective assessment of individual symptoms. Diarrhoea was reduced to a similar degree in both groups, and was improved in 66% of the enema group and 80% of the foam group. However,

to the patient with colitis, the most depressing and disabling symptom is urgency of defaecation, with a tendency to precipitate incontinence, rather than the actual number of times that the bowels are open per day, and this symptom is as frequent in patients with localised proctitis as in those with more extensive disease.² Urgency was relieved in a similar proportion of patients by both modes of treatment, but was unaffected in about 30% in each group.

Many patients have difficulty in retaining the traditional aqueous enema,¹² and it has been claimed that this is not a problem with the foam preparation.¹³ The present study has confirmed this observation, as none of the patients receiving the foam reported any difficulty with retention, whereas eight patients receiving the traditional enemas had difficulty in retaining the morning treatment, and in four this interfered with their ability to go about their normal morning tasks of housework, shopping, or going to work. It might be expected that difficulty in retaining the medication would be associated with a poor response to treatment, but this was not confirmed by separate analysis of the subgroup who experienced this problem. Difficulty in retaining the enema is a nuisance to the patient, but does not appear to prejudice his chance of improvement.

In view of the close similarity in objective response between the two types of treatment, as assessed by the physician, it is surprising to find important differences in the patients' own global assessment of improvement. Such an assessment clearly takes account of many factors not easily measured, and perhaps of varying clinical importance, but they cannot be disregarded, as the main objective of treating colitis is to make the patient's life more tolerable. All except one patient in the foam group considered that he had been improved by the treatment, irrespective of improvement in measured parameters, whereas six patients treated with the traditional enemas considered that no overall improvement had occurred. It is difficult to explain this difference, but expectation of improvement from a 'new' and previously untried treatment may be a factor. However, those patients who had been treated with both preparations expressed an overwhelming preference for the foam, and, despite the fact that the majority of patients in both groups reported no discomfort or difficulty with insertion, it may be that advantages not revealed by this study, in addition to problems in retaining the conventional enema, make the foam preparation more acceptable to the patient.

There is a long tradition of intrarectal medication in colitis, although the recommended therapeutic ingredients have changed since Sir Arthur Hurst advised instillation of tannic acid or hydrogen

peroxide.¹⁹ Rectal hydrocortisone in aqueous solution induces remission in the majority of patients with active proctosigmoiditis. A suspension of hydrocortisone in an inert foam base appears to be equally effective, and is preferred by many patients. The two preparations are similar in cost per unit of treatment.

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