

Fluticasone propionate in Crohn's disease

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Abstract

Fluticasone propionate, a topically active corticosteroid of low systemic bioavailability after oral administration, has been used in a pilot study for the treatment of mild and moderately active Crohn's disease. Twelve patients received oral fluticasone propionate for three weeks, and the effects were monitored using the Crohn's disease activity index and by ^{111}In granulocyte scanning, assessing inflammation from scan appearances, four day faecal excretion of radioactivity, and whole body excretion of radioactivity. All patients completed the trial. No serious side effects were reported. There was a significant fall in Crohn's disease activity index values over the three week treatment period (193 (84) *v* 122 (51), $p < 0.01$). ^{111}In leucocyte scan images were improved (seven patients) or unchanged (five patients). There was a significant fall in excretion of injected radioactivity calculated from whole body data (28 (21)% *v* 14 (0.7)%, $p < 0.05$). There were no changes in plasma cortisol values, either basal or synacthen stimulated. Fluticasone propionate is a promising therapeutic agent for Crohn's disease that offers the possibility of controlling inflammation without inducing systemic corticosteroid side effects and which merits evaluation in a double blind trial *versus* conventional corticosteroids.

As the aetiology of Crohn's disease is still unknown, its management is empiric. Because of their anti-inflammatory and immunosuppressive properties, corticosteroids are widely used in treating active symptomatic disease affecting both the small and large bowel and they are of proved effectiveness in double blind controlled trials.¹ Side effects associated with their use are, however, common and dose related.

Fluticasone propionate is a fluorinated topically active corticosteroid, of low systemic bioavailability when given orally. This may reflect a combination of poor absorption from the gastrointestinal tract and substantial first pass metabolism. In a preliminary study repeat doses of up to 16 mg per day seemed to be well tolerated and did not induce significant hypothalamo-pituitary-adrenal axis suppression in normal volunteers. Side effects would therefore be expected to be less than with conventional steroid treatment.

The purpose of this study was to evaluate the safety and efficacy of fluticasone propionate for the treatment of active Crohn's disease.

Methods

This study was approved by the Hammersmith Hospital Ethics Committee. Twelve patients (six men and six women) aged between 23 and 65

years, with symptomatic relapse of Crohn's disease, were studied. Eleven of the 12 patients had been treated with prednisolone during previous episodes of relapse. Written informed consent was obtained from each patient. All patients had laboratory evidence of active inflammation. Patients were not included if the disease was of sufficient severity to require admission to hospital or had complications that might require surgery. Women who were pregnant or breast feeding and patients with peptic ulcer, active systemic infections, or hypersensitivity to steroids were excluded, as were patients with evidence of renal, hepatic, cardiovascular, metabolic, or endocrine dysfunction or ileostomies. Corticosteroid therapy during the previous 14 days (in excess of 10 mg per day prednisolone equivalent) was also an exclusion criterion.

ASSESSMENT OF DISEASE ACTIVITY

Disease activity was assessed by clinical and laboratory parameters. The Crohn's disease activity index (CDAI) was calculated weekly according to standard procedures,² with a patient diary card being issued to each patient. A ^{111}In white cell scan, ^{111}In faecal excretion, and ^{111}In whole body counting were carried out in all patients before and after treatment.^{3,4} C reactive protein was measured by immunoelectrophoresis and the erythrocyte sedimentation rate by the Westergren technique.

^{111}In WHITE CELL LABELLING

Pure granulocytes were labelled. For this purpose 102 ml of whole blood were drawn from each patient. Granulocytes were isolated by sedimentation on discontinuous plasma enriched density gradient columns and then labelled with 300 mCi (11 MBq) of ^{111}In -tropolonate.⁵ The patient was then reinjected with the labelled granulocytes and between three and four hours after reinjection, anterior and posterior liver and spleen and anterior and posterior abdominal images were taken using a gamma camera (IGE400A or 400T). At 21 to 24 hours the patient returned for the late images. The images were graded by a qualified nuclear physician, unaware of the other data, as negative (0), mildly positive (1+), moderately positive (2+), and markedly positive (3+).⁶

^{111}In FAECAL EXCRETION

After administration of ^{111}In labelled cells, patients were requested to make a four day faecal collection. The total ^{111}In content was counted in an ARMAC gamma counter and the percentage of injected ^{111}In dose was calculated. Faecal ^{111}In excretion of more than 2% of the injected dose is abnormal.³

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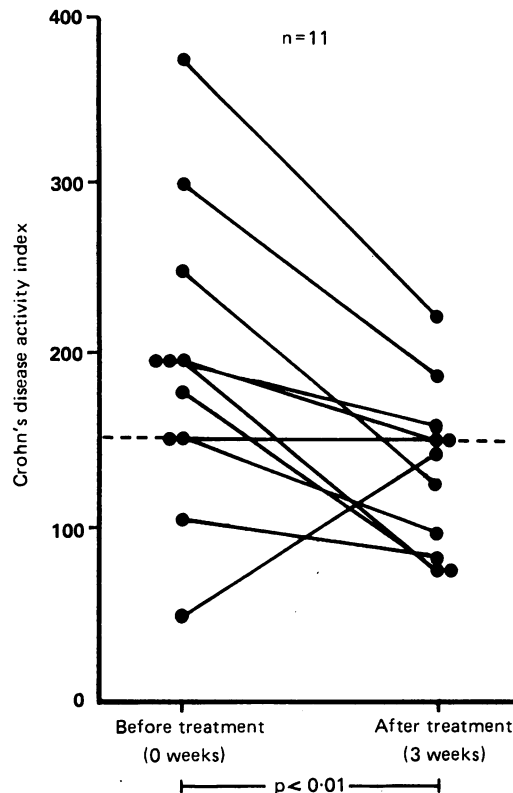


Figure 1: Change in Crohn's disease activity index after three weeks' treatment with fluticasone propionate.

¹¹¹In WHOLE BODY COUNTING

One to three hours after injection of ¹¹¹In labelled granulocytes, the patient stood in front of an uncollimated gamma camera (distance of 3.5 m) and was counted over two minutes. The geometric mean of anterior and posterior counts was taken and compared with the counts from an ¹¹¹In standard, counted at the same distance. The patient returned five to seven days later for the final whole body count. The percentage of the injected ¹¹¹In which was retained was calculated. The results were expressed as 100 whole body retention (WBR) to indicate the excretion of ¹¹¹In. A value greater than 10% is abnormal.⁴

Study protocol

PRESTUDY PHASE

Seven to 10 days before treatment each patient underwent clinical characterisation, which included physical examination and assessment of disease activity by means of clinical and laboratory parameters. The CDAI was calculated and the erythrocyte sedimentation rate and serum C reactive protein were measured. White cell scanning, faecal excretion of ¹¹¹In, and whole body retention of ¹¹¹In were assessed in every patient during this phase. The adrenocortical function was investigated in all patients at the end of this phase. Plasma cortisol concentrations were measured at baseline and a short synacthen stimulation test was carried out in all cases.

DRUG ADMINISTRATION PERIOD

This phase spanned three weeks during which patients were treated with 20 mg/day of flutica-

some propionate, administered orally in four divided doses. Clinical and laboratory parameters were assessed weekly. At the end of this phase a repeat white cell scan, faecal excretion, and whole body retention were carried out in order to assess the efficacy of fluticasone. Plasma cortisol concentrations were again measured and a second synacthen test was also performed.

TAIL OFF PERIOD

The medication was gradually tailed off over a period of nine days and patients underwent safety assessment seven to 14 days after the end of the drug administration.

ASSESSMENT OF DRUG EFFICACY

Efficacy of treatment was assessed by clinical and laboratory parameters as well as by ¹¹¹In labelling techniques.

STATISTICS

The paired Student's *t* test was used to assess the significance of changes resulting from fluticasone treatment.

Results

CLINICAL DETAILS

All twelve patients that entered the trial completed the study.

CDAI was >150 in nine patients at the beginning of the study. The remaining two had scores <150. Mean CDAI values were 193 (84) before treatment and 122 (51) at the end of the

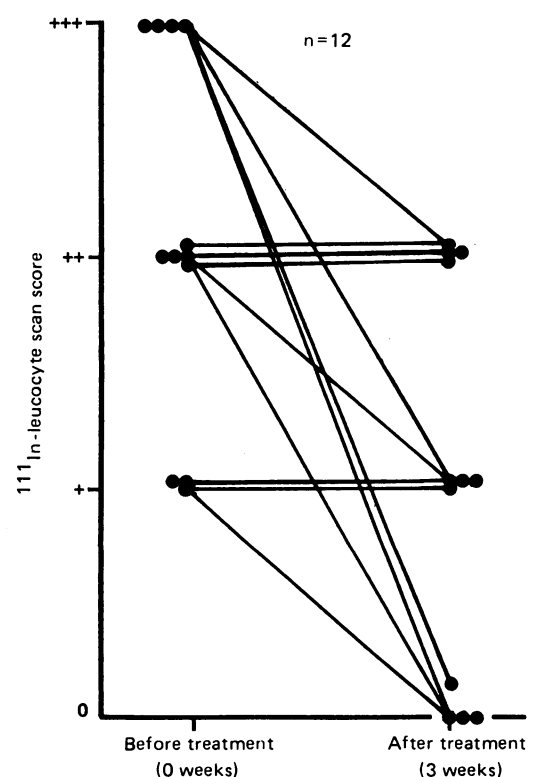


Figure 2: Change in ¹¹¹In leucocyte scan score after three weeks' treatment with fluticasone propionate.

third week of treatment with fluticasone propionate (Fig 1). The difference was statistically significant ($p < 0.01$).

LABORATORY FINDINGS

The serum C reactive protein was abnormal in six patients before treatment and in five patients after it (median 10 v 2). The mean erythrocyte sedimentation rate was 20 (14.3) mm/hour at the beginning of the trial and 17.0 (11.7) (not significantly different) at the end.

¹¹¹In SCAN IMAGING

All patients had active inflammation seen on scan before treatment. After treatment with fluticasone propionate, seven patients no longer had abnormal distribution of activity; inflammatory activity was still present in the scans of five patients, one of whom had less activity than previously (Fig 2).

¹¹¹In FAECAL EXCRETION

Before the trial abnormal ¹¹¹In excretion was recorded in six patients, after three weeks of treatment six patients still showed a faecal loss of ¹¹¹In >2% of the injected dose. Mean values were 17 (32)% v 2.3 (2)%; $p = NS$.

¹¹¹In WBR

¹¹¹In WBR was abnormal in nine of the 12 active patients at the beginning of the study – that is, in those nine patients, over 10% of injected radioactivity had been lost from the body after five to

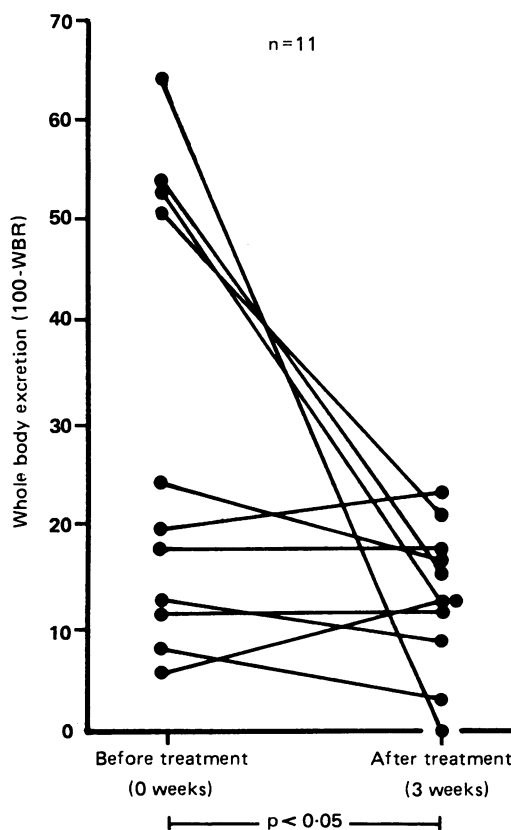


Figure 3: Whole body excretion (100-WBR) after injection of ¹¹¹In labelled leucocytes.

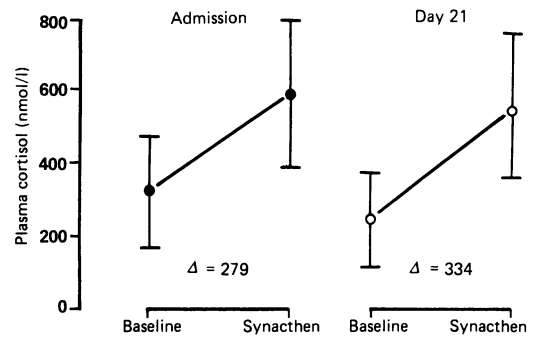


Figure 4: Short synacthen tests before and after treatment for three weeks with fluticasone propionate.

six days. The mean value for the whole body excretion was 28 (21)%. After fluticasone propionate treatment there was a reduction in excretion in seven patients with an over all mean value of 14 (7)% ($p < 0.05$) (Fig 3).

Pretreatment, plasma cortisol values were 320 (162) nmol/l, rising to 600 (210) nmol/l at 30 minutes after synacthen. Corresponding values after treatment were 258 (128) and 574 (201), indicating no change in the mean value or responsiveness (Fig 4).

No serious side effects were reported by any patient. Moderate hyperglycaemia was detected in one patient and resolved spontaneously in one week. On follow up over six months after finishing treatment with fluticasone propionate, six patients had experienced relapse, needing further treatment with conventional corticosteroids.

Discussion

Although corticosteroids are effective treatment for Crohn's disease, side effects are frequently associated with their use. In the multicentre national cooperative Crohn's disease study,^{7,8} prednisolone given orally (0.5–0.75 mg/kg body weight) for 17 weeks caused significant side effects (moon face, acne, ecchymosis, hypertension) in over 50% of patients when used to treat active disease. Side effects were seen in approximately a third of patients when lower doses were used in an attempt to maintain remission (0.25 mg/kg body weight). Long term administration of prednisolone also resulted in a significant rise in blood leucocyte and haematocrit values.

A more recent study evaluated the incidence of osteoporosis in patients with inflammatory bowel disease and reported that 30% of the patients studied were osteoporotic.⁹ Those at highest risk were patients with long standing severe small intestinal disease; intestinal resection; secondary amenorrhoea or premature menopause; and those on high dose steroid therapy. There was a clear negative correlation between lifetime steroid dose and bone mineral content. Another study reported that 4.3% of patients treated with corticosteroids for inflammatory bowel disease over a 10 year period developed osteonecrosis.¹⁰

The diversity and severity of side effects has stimulated the development of different approaches to steroid treatment. The use of an alternate day regime of 40 mg prednisolone orally¹¹ was shown to maintain remission in patients with frequently relapsing ulcerative

colitis. Even then mild side effects attributable to prednisolone were seen after three months of treatment. The use of alternate day therapy has been suggested in Crohn's disease, but there are no controlled trials assessing its value.

New steroid compounds with low systemic bioavailability may provide a major advance in the treatment of inflammatory bowel disease. Such low systemic bioavailability might result from low absorption after oral or rectal administration, rapid first pass metabolism in the gut or liver, or rapid excretion. Several compounds have been or are being assessed. Budesonide,¹² given intrarectally, proved superior to prednisolone enemas in treating active distal ulcerative colitis, using histological and endoscopic assessments. Kumana *et al.*¹³ used beclomethasone dipropionate enemas for treatment of inflammatory bowel disease and showed that they were as effective as betamethasone with virtually no effect on the hypothalamo-pituitary-adrenal axis. A later comparative study of beclomethasone dipropionate enemas *versus* 30 mg prednisolone enemas confirmed the lack of effect of beclomethasone in altering parameters of the hypothalamo-pituitary-adrenal axis after four weeks of treatment, while prednisolone caused a significant fall in morning plasma cortisol concentration and a reduced increase in cortisol in response to the administration of synacthen.¹⁴ Tixocortol pivalate, derived from cortisol has also been used as an enema¹⁵ and shown not to induce changes in plasma cortisol concentrations. Its therapeutic efficiency was not high, however, and it has not been compared with other steroids.

Fluticasone propionate is a fluorinated glucocorticosteroid. Metabolic studies using labelled and unlabelled compounds systemically in rats showed a distribution and elimination from tissues and plasma very similar to other steroids. The blood clearance of fluticasone propionate can be approximated to liver blood flow, with the hepatic extraction ratio approaching unity. The systemic bioavailability of orally administered fluticasone propionate thus tends towards zero as a consequence of extensive hepatic first pass metabolism. In addition, the drug is poorly absorbed from the gastrointestinal tract. The unabsorbed steroid after oral dosing is therefore available in both the small and large intestine to exert local actions.

In this study an oral daily dose of 20 mg fluticasone propionate seemed effective in treating mild and moderately active small intestinal and colonic Crohn's disease, the effects being apparent within three weeks of treatment. Significant improvement was shown in clinical symptoms, as measured by the CDAI and quantification of active inflammation from ¹¹¹In leucocyte scan appearances and whole body excretion data. The results of the faecal excretion data are discussed below. The efficacy of fluticasone propionate is supported by the observation that on follow up 58% of the patients had a relapse within one to six months of stopping the treatment, and required treatment with conventional steroids.

The absence of serious side effects and the unchanged plasma cortisol values before and after treatment, confirmed that there was

no significant depression of the hypothalamic-pituitary-adrenal axis, suggesting that the therapeutic effect was exerted locally.

This outpatient study, however, highlighted a problem in using faecal excretion of ¹¹¹In to assess changes in inflammation. The results obtained, with in many cases high values of ¹¹¹In excretion on whole body counting but low values in faecal collections, clearly showed that faecal collections are often incomplete. This study in combination with observations on other patients⁴ has shown that whole body retention can be used as a simpler and more accurate technique for quantitating excretion. This method is also more aesthetically acceptable.

It was of interest that the clinical and labelled leucocyte based assessments were not associated with changes in C reactive protein and erythrocyte sedimentation rate values, although neither of these were initially strikingly abnormal in this group of patients with mild or moderately active disease. Increases in these parameters reflect enhanced synthesis of acute phase reactants by the liver,¹⁰ and it may be that poorly absorbed steroids have less effect on this aspect of the immune response than they do on local inflammatory responses within the gut.

As this study has suggested that fluticasone propionate may be effective, a randomised trial of this *versus* prednisolone is now indicated. The value of such a non-absorbable steroid would not only be in the treatment of active disease, but also for maintenance treatment. The European cooperative Crohn's disease study¹ highlighted the value of 6-methyl prednisolone in a low dose regimen for periods up to two years for patients who entered remission on steroid therapy, and the potential for avoiding systemic side effects during such long term treatment warrants exploration.

- 1 Malchow H, Ewe K, Brandes JW, *et al.* European Cooperative Crohn's Disease study (ECCDS): results of drug treatment. *Gastroenterology* 1984; 86: 249-66.
- 2 Best WR, Beckett JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's disease activity index (CDAI). *Gastroenterology* 1979; 77: 843-6.
- 3 Saverymuttu SH, Peters AM, Lavender JP, Hodgson HJF, Chadwick VS. ¹¹¹Indium autologous leucocytes in inflammatory bowel disease. *Gut* 1983; 24: 293-9.
- 4 Peters AM, Saverymuttu SH, Reavy HJ, Danpure HJ, Osman S, Lavender JP. Imaging of inflammation with ¹¹¹Indium tropolonate labelled leukocytes. *J Nucl Med* 1983; 24: 39-44.
- 5 Carpani M, Peters AM, Hodgson HJF, Knight D, Lavender JP. Quantification of whole body granulocyte excretion in inflammatory bowel disease. *Nucl Med Commun* 1989; 10: 267.
- 6 Saverymuttu SH, Camillieri M, Rees H, Lavender JP, Hodgson HJF, Chadwick VS. Indium ¹¹¹-granulocyte scanning in the assessment of disease extent and disease activity in inflammatory bowel disease: a comparison with colonoscopy, histology, and faecal Indium ¹¹¹-granulocyte excretion. *Gastroenterology* 1986; 90: 1121-8.
- 7 Summers RW, Switz DM, Sessions JT, *et al.* National cooperative Crohn's disease study: results of drug treatment. *Gastroenterology* 1979; 77: 847-69.
- 8 Singleton JW, Law DH, Kelley ML, Jr, Mekhjian HS, Sturdevant RAL. National cooperative Crohn's disease study: adverse reactions to study drugs. *Gastroenterology* 1979; 77: 870-82.
- 9 Compston JE, Judd D, Crawley EO, *et al.* Osteoporosis in patients with inflammatory bowel disease. *Gut* 1987; 28: 410-5.
- 10 Vakil N, Sparberg M. Steroid-related osteoporosis in inflammatory bowel disease. *Gastroenterology* 1989; 96: 62-7.
- 11 Powell-Tuck J, Brown RL, Chambers TJ, Lennard-Jones JE. A controlled trial of alternate day prednisolone as a maintenance treatment for ulcerative colitis in remission. *Digestion* 1981; 22: 263-70.
- 12 Danielson A, Hellers G, Lyrenas E, *et al.* A controlled

- randomised trial of Budesonide versus Prednisolone retention enemas in active distal ulcerative colitis. *Scand J Gastroenterol* 1987; 22: 987-92.
- 13 Kumana CR, Meghji M, Seaton T, Castelli M. Beclomethasone dipropionate enemas for treating inflammatory bowel disease without producing Cushing's syndrome or hypothalamic pituitary adrenal suppression. *Lancet* 1982; i: 579-83.
 - 14 Van der Heide H, van den Brandt-Gradel V, Tytgat GNJ, *et al.* Comparison on beclomethasone dipropionate and prednisolone 21-Phosphate enemas in the treatment of ulcerative proctitis. *J Clin Gastroenterol* 1988; 10: 169-72.
 - 15 Larochelle P, Du Souich P, Bolte E, Leloirier J, Goyer R. Tixocortol pivalate, a corticosteroid with no systemic glucocorticoid effect after oral, intrarectal, and intranasal application. *Clin Pharmacol Ther* 1983; 33: 343-50.