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CLINICAL TRIAL

Double blind trial of oral fluticasone propionate *v* prednisolone in the treatment of active ulcerative colitis

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Abstract

Fluticasone propionate is a corticosteroid with the potential for topical treatment of ulcerative colitis because of low systemic bioavailability. The drug was compared with prednisolone in the management of active left sided or total ulcerative colitis. Two hundred and five patients were studied in the multicentre four week double blind study. Prednisolone was given in a dose of 40 mg daily orally, reducing over four weeks to 10 or 20 mg. Fluticasone propionate was given in an oral daily dose of 20 mg. The primary end point was the investigator's overall assessment of response. Patient's assessment, sigmoidoscopic appearance, and histology were also studied. Patients improved more rapidly with prednisolone. Differences between the two groups were significant at two weeks. At four weeks differences were not significant, but there was a trend in favour of prednisolone. Corticosteroid side effects were minimal in the fluticasone propionate group, and there was minimal suppression of the hypothalamic pituitary adrenal axis. Fluticasone propionate 20 mg daily is not as effective in the treatment of active ulcerative colitis as prednisolone tapering from 40 mg daily to 10 or 20 mg. The complete absence of suppression of the corticoadrenal axis by fluticasone propionate was encouraging, however, and a higher dosage schedule should be assessed.

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Corticosteroid drugs are the most effective and widely used treatment for acute relapse of ulcerative colitis. High dosage or prolonged treatment is associated with a range of side effects. Topically active corticosteroids, with reduced systemic bioavailability, should have fewer side effects, and there is evidence that enema preparations of corticosteroid drugs with metabolism in gut wall or liver are effective in distal colitis.[1-3]

Fluticasone propionate is a potent topically active fluorinated corticosteroid with low systemic bioavailability after oral administration, partly because of malabsorption, and partly because of extensive first pass metabolism. A significant proportion of the drug reaches the colon. This study was designed to compare the efficacy and safety of oral fluticasone propionate with prednisolone over a four week period in the treatment of active colitis.

Methods

The study was a multicentre randomised double blind parallel group trial of oral fluticasone propionate (5 mg four times daily) *v* prednisolone in reducing dosage. Ethical committee approval was obtained from 24 participating centres in the United Kingdom and Eire, and informed written consent was obtained from patients.

PATIENTS

The patients studied had active ulcerative colitis affecting at least the left side of the colon. Outpatients, with three or more bowel actions daily, passing liquid or semiformed stool were considered for trial entry. Patients who had taken corticosteroids in a daily dosage equivalent to 10 mg or more of prednisolone orally, or 20 mg rectally in the previous 14 days were not included. The other major exclusion criteria were Crohn's disease, pregnancy, or concomitant serious medical conditions.

TREATMENT

All patients received two tablets four times a day. Patients randomised to prednisolone received 40 mg daily for week one and 30 mg daily for week two. At 14 days all patients were reassessed, and if improving were assigned to treatment option A: prednisolone 20 mg daily for week three and 10 mg daily for week four. If there was no improvement they were given treatment B: 30 mg daily for week three and 20 mg daily for week four. Patients in the fluticasone propionate group received 5 mg four times daily throughout the trial, regardless of whether they were allocated to group A or group B at 14 days.

TRIAL ASSESSMENTS

Patients were seen weekly and kept a daily symptom diary. Sigmoidoscopy and rectal biopsy was performed at entry, day 14, and day 28. Mucosal appearance was graded from zero to

three according to Baron *et al*,[4] and histological appearance and vascularity scored as described by Powell-Tuck *et al*.[5] Blood pressure, blood count, biochemical profile, and urine tests were checked at entry, day 7, 14, and 28, and plasma cortisol, measured by high performance liquid chromatography, at entry, day 14, and 28. Blood tests were also performed two weeks after trial completion.

END POINTS

The primary end points were ascertained at day 28 as (*a*) the investigator's overall assessment of the patient's condition compared with pretreatment, 'investigator's assessment', (*b*) the patient's assessment of remission as recorded in the diary card, 'patient's assessment', and (*c*) the sigmoidoscopy score.

STATISTICAL ANALYSIS

The main analysis was on an intention to treat basis and included all patients randomised. A subsidiary analysis evaluated those patients adhering fully to the protocol. The trial was designed to have an 80% power, with significance set at the 5% level. Using the end point of investigator's assessment of remission, it was calculated that 226 patients were required to show that fluticasone propionate was at worst 15% inferior to prednisolone. Two hundred and six patients in all were enrolled, and 159 patients were included in the analysis, according to protocol, sufficient to show that fluticasone propionate was no more than 18% inferior to prednisolone. Overall results, with the exclusion of a patient with *Campylobacter jejuni* infection, were analysed for safety. Assessments were made at two and four weeks for each treatment group and compared after adjusting for pretreatment values, using the Mantel-Haenzel unadjusted χ^2 test, with modified ridit scores. The investigator's overall assessments were also compared for the two treatments after adjusting for sex, initial disease severity, hospital centre, and treatment option at day 14.

TABLE I *Baseline entry characteristics*

	Fluticasone (n=100)	*Prednisolone (n=105)*
No (%) men	51 (51)	51 (49)
Median age (range)	41 (18–72)	40 (19–68)
Duration of colitis, months; median (range)	70 (1–360)	60 (1–324)
Duration of current exacerbation, weeks; median (range)	4 (1–96)	6 (1–96)
No (%) taking sulphasalazine	45 (45)	46 (44)
No (%) taking mesalazine	23 (23)	16 (15)
Entry sigmoidoscopy score (No (%))		
0	1 (1)	0 (0)
1	10 (10)	7 (7)
2	46 (46)	55 (52)
3	43 (43)	43 (41)
Initial assessment of disease activity (No (0%))		
Mild	9 (9)	7 (7)
Moderate	70 (70)	76 (72)
Severe	19 (19)	16 (15)
Extremely severe	0 (0)	2 (2)

No significant differences between treatment groups.

TABLE II *Clinical results (intention to treat analysis)*

	Week 2		*Week 4*	
	Fluticasone	*Prednisolone*	*Fluticasone*	*Prednisolone*
Investigator's overall assessment (No (%))	(n=98)	(n=101)	(n=98)	(n=100)
In remission	9 (9)	17 (17)	25 (26)	29 (29)
Improved	48 (49)	59 (58)	36 (37)	48 (48)
No change/worse	41 (42)	25 (25)	37 (38)	23 (23)
	p=0·007		p=0·087	
*Sigmoidoscopic appearance** (No (%))	(n=95)	(n=94)	(n=97)	(n=99)
Grade 0 or 1	36 (37)	47 (50)	48 (49)	62 (62)
	p=0·008		p=0·028	

*Data missing in some patients owing to withdrawal or non-compliance.

Results

Two hundred and six patients entered the study; 101 received fluticasone propionate and 105 prednisolone. One patient was found to have *Campylobacter jejuni* infection, and was excluded from all analyses. Forty six patients were excluded from the analysis according to protocol, 42 because of incorrect entry requirements (15 taking steroids at too high a dose at entry, 21 because symptoms were too mild, and six because disease extent was not established). Four of the withdrawals (see below) were excluded. A further 10 patients were partially excluded because of non-compliance, use of disallowed drugs, or late or early clinic visits. This left 73 patients receiving fluticasone propionate and 86 prednisolone in the analysis according to protocol.

Thirty one patients withdrew during the trial: four because of adverse events (one receiving fluticasone propionate, three receiving prednisolone), 24 because of lack of improvement (12 in each group), one receiving fluticasone propionate because of poor compliance, one who did not complete the trial, and another because of a positive pregnancy test (both receiving prednisolone).

Patients' baseline characteristics were similar in both groups, as shown in Table I.

EFFICACY

Data presented are from the intention to treat analysis. Data from patients adhering fully to the protocol were also analysed, and where results differ, these are also presented. The investigator's assessment is shown in Table II. At two weeks there was a significant difference in favour of prednisolone, but at four weeks the difference was no longer significant.

Specific symptoms were significantly better on prednisolone at two and four weeks, compared with fluticasone propionate. Fifty two per cent of patients receiving prednisolone had formed stools after four weeks, compared with 29% receiving fluticasone propionate (p=0·007); 60% had no bleeding, compared with 45% for the fluticasone propionate group (p=0·021); and 73% had fewer than three bowel motions a day compared with 41% of those receiving fluticasone propionate (p=0·001). Overall, at the end of the trial, 20% of the fluticasone propionate group considered themselves in complete remission, compared with 39% of the prednisolone group (p=0·003). Results were similar in the analysis according to protocol, with 14% considering themselves in remission in the

TABLE III *9 am plasma cortisol measured by high performance liquid chromotography. Results are shown as mean (SD) plasma cortisol levels in nmol/l*

	Fluticasone propionate (n=33)	*Prednisolone (n=25)*
Pretreatment	306 (182)	310 (208)
Week 2	277 (123)	5·5 (13)
Week 4	303 (139)	57 (105)
	p<0·001	

fluticasone propionate group, compared with 39% in the prednisolone group (p=0·001).

Sigmoidoscopy scores showed significant differences in favour of prednisolone at weeks two and four (Table II) in the intention to treat analysis. In the analysis according to protocol, however, the difference in favour of prednisolone was significant at week two (p=0·021), but not at week four (p=0·12). At week four the histological appearance of the biopsy specimens of 39% of patients receiving prednisolone had improved, compared with 19% in the fluticasone propionate group (p=0·004). Differences in biopsy vascularity did not differ significantly between the two groups at week four.

SAFETY

More corticosteroid associated effects were seen in the prednisolone group: of the 100 patients, seven patients had facial swelling, four had facial flushing, one had confusion, and one increased hair growth. There were no such effects in the fluticasone group.

At entry, blood pressure was similar in both groups. At four weeks, systolic pressure was 129 (18) mm Hg (mean (SD)), diastolic pressure 80 (12) mm Hg for the prednisolone group; *v* 120 (19) mm Hg and 77 (12) mm Hg respectively for the fluticasone propionate group. The difference between the two treatments was significant when adjusted for pretreatment values (p<0·001 systolic, and p=0·048 diastolic). Random plasma glucose rose in 13 of 77 (17%) patients receiving fluticasone propionate, and in 23 of 81 (28%) of those receiving prednisolone. Plasma cortisol levels (measured by high performance liquid chromotography) did not fall significantly in the fluticasone propionate group, although there was marked suppression in the prednisolone group (Table III).

There were no deaths during the study, but two patients died shortly afterwards. A 72 year old woman died of a perforated colon 11 days after completing the trial, despite continuing prednisolone treatment. A 55 year old woman was withdrawn from the study at day 22, and treated with oral prednisolone. Ten days later she was admitted and given intravenous steroids, and died of presumed septicaemia shortly after a laparotomy (day 38). Both had been taking fluticasone propionate during the trial, but the investigators considered the deaths were caused by disease activity rather than the treatment received.

Discussion

There was improvement in both patient groups during the trial, with 63% and 77% of patients (fluticasone propionate and prednisolone respectively) improved or in remission, as assessed by the investigator at week four. Improvement occurred earlier in the prednisolone group, and at two weeks there was a significant difference in the investigator's assessments in favour of prednisolone. At four weeks the difference was no longer significant. It is possible that the closure of the efficacy gap at four weeks was because of the reduction in dosage in the prednisolone group, but also because fluticasone propionate acted more slowly. Overall, however, there was a trend for prednisolone to be more effective than fluticasone propionate. Sigmoidoscopic appearance and patients' symptoms were significantly better in the prednisolone group at two and four weeks. Biopsy inflammation score was significantly better, but vascularity score did not differ between the two treatments. Data from the 159 patients adhering fully to the protocol gave similar conclusions.

The majority of side effects were minor, but there was a marked absence of corticosteroid effects and hypothalamic pituitary adrenal axis suppression in the fluticasone propionate group. The two deaths after the trial were related to severe ulcerative colitis, and unlikely to have been drug related.

There are virtually no placebo controlled trials of acute relapse of extensive ulcerative colitis with which to compare these results, and such a trial would be unethical. There is little doubt that a response rate of 63% for the fluticasone group does represent a therapeutic effect. A placebo controlled study has, however, been carried out in active distal ulcerative colitis by Angus *et al*,[6] and showed that the drug was not significantly better than placebo. The trial was, however, relatively small (59 patients) raising the possibility of a type two error, and it is possible that fluticasone propionate was not present in sigmoid colon and rectum and thus could not have a therapeutic effect (two thirds of patients had rectosigmoid disease only). It is likely that the drug would be more effective in the proximal colon.

It is possible that the relative lack of efficacy of fluticasone propionate compared with a standard regimen of prednisolone is because the dose chosen was too low to produce therapeutic concentrations in the colon. The daily dose of 20 mg was chosen on the basis of volunteer studies, where doses of 10 mg and 20 mg four times daily suppressed the hypothalamicpituitary axis, whereas 5 mg four times a day did not (Glaxo Group Research Ltd, unpublished data). The degree of colonic bioavailability might have been insufficient for other reasons. Plasma concentrations after oral dosage vary widely from individual to individual, and after a single 16 mg dose, recovery in the stool varies from 14 to 49% in volunteers (Glaxo Group Research Ltd, unpublished data). Thirdly, more prolonged treatment might have shown a late effect.

Although it may not be possible to achieve therapeutic effects in the colon with this formulation, small bowel luminal concentration may be higher, and might account for the reports of possible benefit in small numbers of patients with coeliac and Crohn's disease.[7,8] A larger trial

in Crohn's disease is being evaluated. Although side effects in our study were minimal, oral fluticasone propionate 5 mg four times daily was not as effective as prednisolone in standard doses in the treatment of ulcerative colitis. Further studies to find a more effective topically active oral preparation are needed.

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