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Beclomethasone dipropionate enemas versus prednisolone sodium phosphate enemas in the treatment of distal ulcerative colitis

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SUMMARY

Aim: To compare beclomethasone dipropionate 3 mg/60 mL enema (BDP) and prednisolone sodium phosphate 30 mg/60mL enema (PP) once daily in patients with active distal ulcerative colitis.

Methods: One hundred and fifty-seven patients were enrolled in a multicentre, 4-week, randomized, double-blind trial. Patients were assessed at baseline, 2 and 4 weeks.

Results: Both treatment groups showed statistically significant improvement of clinical activity after 2 and 4 weeks. Endoscopy and biopsy showed a reduction in the activity score at the end of the treatment period in both groups. No statistically significant difference was observed between the two treatment groups. After 4 weeks, 29% of patients in the BDP group and 25% in the PP group were considered to be in clinical remission; an improvement was observed in 40% of patients on BDP and in 47% on PP. Mean morning plasma cortisol levels showed a slight but significant reduction in the PP group, while the ACTH test showed that neither drug interfered with the hypothalamic–pituitary–adrenal (HPA) axis function. No significant changes were observed in the laboratory tests. Finally, there was a low incidence of adverse events in both groups.

Conclusions: It is concluded that, in the topical treatment of active distal ulcerative colitis, BDP 3 mg enemas are as efficacious as PP 30 mg enemas, without interference with the HPA axis.

INTRODUCTION

Topical treatment of active distal ulcerative colitis (UC) with enemas containing glucocorticosteroids is well established,[1–4] but prolonged use is limited by the risk of systemic adverse effects, such as suppression of the hypothalamic–pituitary–adrenal (HPA) axis function.[5–8] In order to avoid adrenocortical dysfunction, it would seem preferable to treat UC with new topical corticosteroids, characterized by low systemic availability and high topical activity.[9, 10]

Beclomethasone dipropionate (BDP) is a topical corticosteroid that effectively treats asthma and allergic rhinitis.[11–13] It is a potent glucocorticosteroid characterized by local anti-inflammatory activity with minimal systemic activity and adverse effects.[14] Several controlled studies have shown that BDP enemas are as effective or more effective than systemic glucocorticosteroids

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for the treatment of distal UC,[15] and that treatment does not interfere with the HPA axis, in contrast to treatments with topical betamethasone [16, 17] or prednisolone sodium phosphate (PP).[18] The lack of interference of BDP enemas with adrenocortical function indicates that the absorption of this drug is insignificant or that its intestinal or hepatic metabolism is very rapid.[9, 19]

The aim of our investigation was to compare the efficacy of BDP 3 mg/60 mL enemas with prednisolone sodium phosphate 30 mg/60 mL (PP) enemas, administered once daily, in patients with active distal UC, and to evaluate the influence of treatments on adrenocortical function.

MATERIALS AND METHODS

Patients

From February 1990 to March 1992, 157 outpatients with active distal UC, which was localized to the distal 15–50 cm of the colon, participated in this randomized, double-blind trial, performed in nine centres in Italy. Patients were eligible if they had rectal bleeding during the week prior to entry and a diagnosis of UC confirmed clinically, endoscopically (to determine the extent and the severity of disease) and histologically (to assess the severity of inflammation) before admission. Patients with total colitis, anal or peri-anal lesions, severe renal or hepatic failure, diabetes mellitus, gastroduodenal disease, severe hypertension, pregnancy, or undergoing treatment with corticosteroid medications for at least 1 month prior to entering the trial, were excluded. Oral or rectal treatment with steroid medications, apart from the study drugs, was not allowed during the study. Continued oral sulphasalazine (SASP) and mesalazine (5-ASA) use was allowed only if they had been taken during the 2 weeks before entry, and the daily doses had to be kept constant during the study period.

The trial was performed in accordance with the Declaration of Helsinki and it was approved by local Ethics Committees. Written informed consent was obtained from each patient before entry into the study.

Study drugs

Enemas were supplied by Chiesi Farmaceutici S.p.A. (Parma, Italy). They contained either BDP 3 mg or PP 30 mg and sterilized water to give a total volume of 60 mL. Both preparations were identical in appearance and were dispensed in a plastic bottle fitted with a rectal cannula. The enemas were provided in identical blister packages which were returned by the patients at each clinic visit. The enemas were administered once daily at bedtime. Compliance was checked by the study personnel by counting the returned unopened and opened blister packs. Patients were considered non-compliant if they had taken less than 75% of the study drug during their treatment period.

Conduct of the trial and assessment of the treatment results

Patients were treated for 4 weeks. To determine the extent and activity of the disease, clinical symptoms and endoscopic findings were assessed at baseline and after 2 and 4 weeks by a scoring system (Table 1). The clinical evaluation took into account daily stool frequency (average), stool consistency, abdominal discomfort, tenesmus, evacuating urgency, rectal bleeding, mucus in the stools and subjective sense of well-being. The endoscopy findings were graded according to Baron's criteria[20] (Table 1). Three pinch biopsy specimens were also taken during endoscopy, from the areas of mucosa judged to be the most severely inflammed. Disease activity was assessed histologically at baseline and after 4 weeks and all biopsy data were interpreted without knowledge of the clinical state of treatment category according to Truelove and Richard's criteria [21] (Table 1). A complete haematochemical evaluation (haematological, liver and renal function tests, glycaemia, total proteins, electrolytes) was carried out on each patient at baseline and after 4 weeks. Cardiovascular parameters (blood pressure and heart rate) were monitored at baseline and after 2 and 4 weeks. Adverse events were recorded and described. Patients were considered to be in remission if they had an endoscopic score of 0 and a clinical score of 0 or 1; improvement was defined as a decrease of at least 1 point in the endoscopic score and at least 2 points in the clinical score. All other patients were considered non-responders.

The effect of treatments on endogenous cortisol production was assessed by measuring plasma cortisol levels. Samples for determination of fasting plasma cortisol concentrations (range 5–25 mg/dL) were drawn at 08.00–10.00 h, before the first enema and 24 h after the last enema, but always at the same time at each visit, and cortisol concentrations were measured by radioimmunoassay. In addition, to evaluate the

Table 1. Assessment of scored clinical, endoscopic and histological activity

Assessment of clinical activity	
Stool frequency (daily average)	Score
Stool consistency:	
Normal	0
Partially formed	1
Semi-liquid	2
Liquid	3
Abdominal discomfort/tenesmus/ evacuating urgency:	
Normal	0
Mild	1
Moderate	2
Severe	3
Rectal bleeding/mucus in stools:	
None	0
Streaks	1
Obvious	2
Mostly	3
Subjective sense of well-being:	
Normal	0
Mild	1
Moderately compromised	2
Severely compromised	3
Endoscopic assessment	
Normal mucosa	0
Hyperaemic mucosa, indistinct vascular pattern	1
Friability, contact bleeding	2
Spontaneous bleeding, ulceration, mucopurulent mucosa	3
Histological assessment	
Normal mucosa	0
Chronic inflammatory cell infiltrate in lamina propria	1
Mild crypt injury with acute inflammatory cell infiltrate, some crypt abscesses	2
Marked crypt destruction with crypt abscesses and ulceration	3

influence of BDP and PP on the HPA axis function, an ACTH test was performed at baseline and after 4 weeks, in 30 patients (15 in the BDP group and 15 in the PP group) to measure the increase in serum cortisol 30 and 60 min after a 250 mg i.v. bolus dose of synthetic ACTH (Synacthten Ciba Geigy). The samples were frozen for later determination of plasma cortisol concentrations. Determination of plasma cortisol concentrations was performed blind.

Statistical analysis

All the patients who received study treatment were included in the analysis. SAS software (version 6.04) was used for data management and statistical analysis. Wilcoxon's rank sum and χ^2 tests were used to evaluate the comparability of the two treatment groups at baseline. The clinical, endoscopic and histological scores were analysed within treatment by Friedman's test; when significant, multiple comparisons with baseline values were performed according to Nemenyi's test. Wilcoxon's rank sum test was used on the changes from baseline in the comparison of the treatments. The ACTH test results were analysed using Wilcoxon's signed rank and rank sum tests in the comparison within and between treatments, respectively. Responses to therapy were compared between treatments using χ^2 tests. Two-tailed significance tests were used. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 157 patients were randomly assigned to receive BDP or PP enemas. The characteristics of the patients at entry were comparable (Table 2). Fifteen patients (9.6%) did not complete the study (Figure 1). Of these patients, eight (5.1%) were withdrawn because of insufficient therapeutic effect, three (1.9%) patients were lost to the follow-up and four (2.5%) patients were withdrawn because of adverse events.

Table 2. Patient characteristics at entry

	BDP ($n = 80$)	PP ($n = 77$)
Age (years)*	41.2 (1.6)	42.2 (1.5)
Sex (M:F)	53:27	48:29
Diagnosis (*n*)		
Proctitis	1	4
Proctosigmoiditis	2	4
Distal ulcerative colitis	77	69
Duration of disease (months)*	85.85 (21.9)	79.89 (8.7)
First episode (*n*)	7	12
Relapse (*n*)	73	65
Previous therapy (*n*)		
Oral mesalazine	33	32
Oral sulphasalazine	27	9
Topical mesalazine	9	6

*Data are expressed as mean (S.E.M).

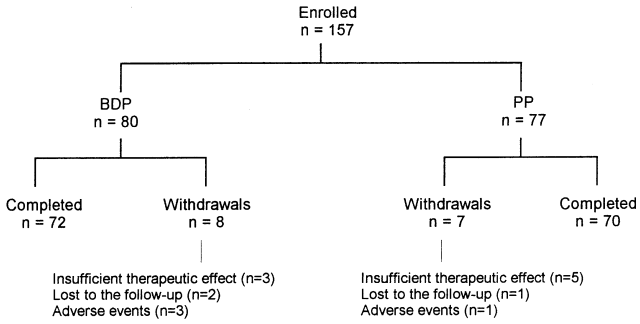

Figure 1. Disposition of patients.

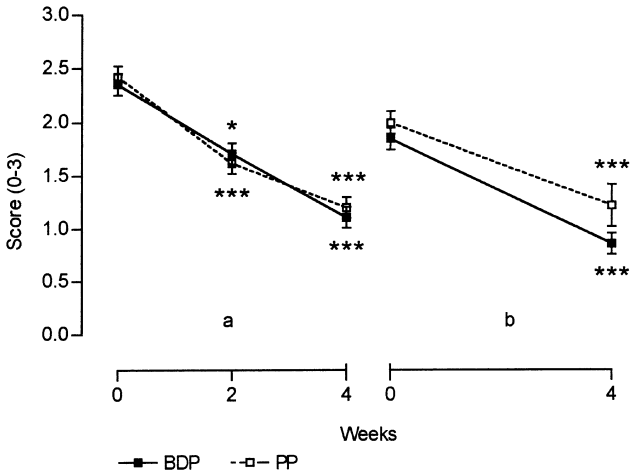

Figure 2. Endoscopic (a) and histological (b) score variations in the BDP group and in the PP group. Data are expressed as mean (S.E.M); * $P < 0.05$ vs. baseline, *** $P < 0.001$ vs. baseline.

Effect of steroidal enemas on colitis

In both groups, a statistically significant improvement in the clinical variables was observed after 2 and 4 weeks (Table 3). The endoscopic score was significantly reduced in both groups at 2 weeks ($P < 0.05$ for the BDP group; $P < 0.001$ for the PP group) and at 4 weeks ($P < 0.001$) (Table 3, Figure 2). A significant reduction ($P < 0.001$) was also observed in both groups with respect to the histological findings at the end of the treatment period (Table 3, Figure 2). No significant difference between the groups was observed. After 4 weeks, 23 (29%) BDP-treated patients and 19 (25%) PP-treated patients achieved clinical and endoscopic remission. An improvement was observed in 32 (40%) patients treated with BDP enemas and in 36 (47%) patients receiving PP enemas.

Effect on adrenocortical function

On entry into the study, all patients in both treatment groups had a baseline plasma cortisol concentration above 5 mg/dL. After 4 weeks, mean plasma cortisol concentration, almost unchanged in the BDP group, showed a slight but significant decrease in patients treated with PP enemas ($P < 0.05$) (Figure 3). None of the treated patients had plasma cortisol levels below 5 mg/dL. On entry into the study and after 4 weeks, patients in which the ACTH test was performed had a normal plasma cortisol value (Figure 4).

Adverse events

Eight (10%) patients in the BDP group and six (8%) patients in the PP group experienced adverse events. Three patients treated with BDP and one patient treated

Table 3. Summary of efficacy results

	BDP			PP		
Weeks	0	2	4	0	2	4
Stool frequency	4.5 (0.3)	3.0 (0.3)[c]	2.6 (0.3)[c]	4.6 (0.3)	2.8 (0.2)[c]	2.5 (0.2)[c]
Stool consistency	1.8 (0.1)	1.1 (0.1)[c]	0.8 (0.1)[c]	1.7 (0.1)	1.1 (0.1)[c]	0.8 (0.1)[c]
Abdominal discomfort	1.3 (0.1)	0.8 (0.1)[b]	0.4 (0.1)[c]	1.4 (0.1)	0.8 (0.1)[b]	0.5 (0.1)[c]
Tenesmus	1.3 (0.1)	0.8 (0.1)[c]	0.5 (0.1)[c]	1.4 (0.1)	0.8 (0.1)[c]	0.4 (0.1)[c]
Evacuating urgency	1.4 (0.1)	0.8 (0.1)[c]	0.5 (0.1)[c]	1.3 (0.1)	0.8 (0.1)[c]	0.5 (0.1)[c]
Rectal bleeding	1.8 (0.1)	1.0 (0.1)[c]	0.6 (0.1)[c]	1.7 (0.1)	1.0 (0.1)[c]	0.6 (0.1)[c]
Mucus in stools	1.6 (0.1)	0.9 (0.1)[c]	0.6 (0.1)[c]	1.7 (0.1)	0.9 (0.1)[c]	0.7 (0.1)[c]
Sense of well-being	0.7 (0.1)	0.5 (0.1)	0.4 (0.1)[a]	0.8 (0.1)	0.6 (0.1)	0.5 (0.1)[a]
Mucosal appearance	2.3 (0.1)	1.7 (0.1)[a]	1.1 (0.1)[c]	2.4 (0.1)	1.6 (0.1)[c]	1.2 (0.1)[c]
Histological findings	1.8 (0.1)		0.9 (0.1)[c]	2.0 (0.1)		1.2 (0.2)[c]

Data are expressed as mean (S.E.M); a = $P < 0.05$ vs. baseline, b = $P < 0.01$ vs. baseline, c = $P < 0.001$ vs. baseline.

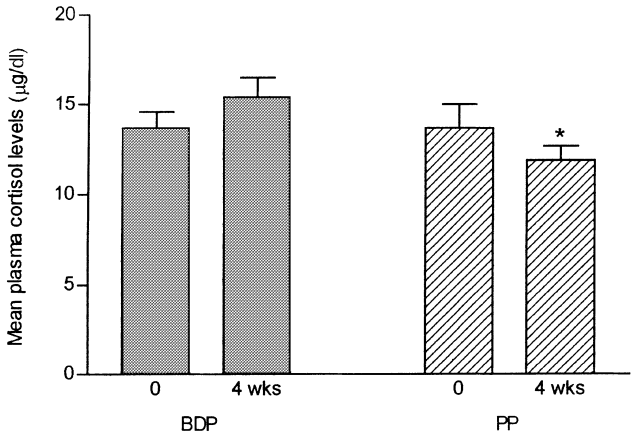

Figure 3. Plasma cortisol levels in the BDP ($n = 23$) and in the PP ($n = 23$) group before and after 4 weeks. Data are expressed as mean (S.E.M); range 5–25 μg/dL; $^*P < 0.05$ vs. baseline.

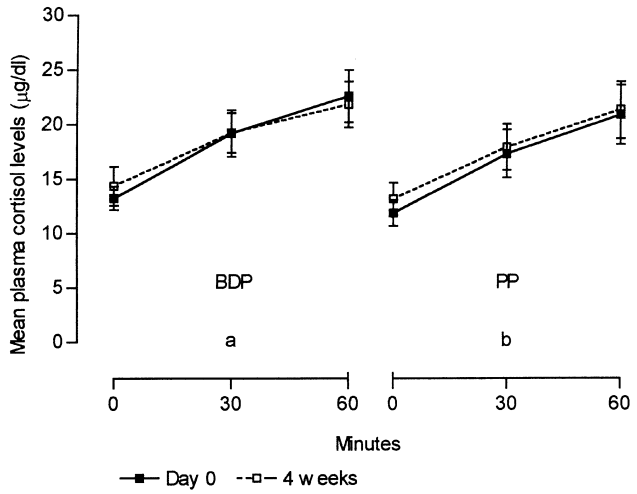

Figure 4. ACTH-stimulated plasma cortisol levels in the BDP ($n = 15$) and in the PP ($n = 15$) group before (a) and after 4 weeks (b). Data are expressed as mean (S.E.M); range 5–25 μg/dL.

with PP were withdrawn from the trial because of adverse events. Two of the three patients withdrawn from the BDP treatment group had rectal incontinence with a burning sensation and one had rectal incontinence. By contrast, only one patient taking PP had to stop treatment because of a burning sensation. In the remaining five patients treated with BDP, one patient reported rectal incontinence, three patients complained of a burning sensation and one had rectal incontinence with a burning sensation. In the PP-treated group, one patient reported rectal incontinence and four patients complained of a burning sensation. None of the patients had pathological alterations in the laboratory tests either at baseline or at the end of the treatment.

DISCUSSION

The present study indicated that BDP 3 mg enemas are as effective as PP 30 mg enemas in the treatment of active distal ulcerative colitis and are well tolerated and safe. Symptomatic remission or substantial clinical improvement was observed in 68.8% of patients receiving BDP and in 71.4% of patients receiving PP after 4 weeks of treatment. Complete control of symptoms was evident in most patients within 2 weeks of therapy; the improvement in mucosal appearance lagged behind symptomatic improvement. Both treatments were well tolerated, although with PP there was a slight but significant decrease in fasting cortisol levels, while no effect was found in patients treated with BDP. However, the cortisol increase after the ACTH test showed no differences before and after therapy in both groups. The lack of suppression of the adrenocortical function determined by BDP enemas is in accordance with the results of previous reports.[15–17].

Topical corticosteroids were first introduced by Truelove[1] and Watkinson.[22] Subsequently, an intrarectal drip of PP has been shown to be efficacious in distal disease.[23] Because of the potential systemic absorption and side-effects, which vary with the dose and duration of the administration, new topical steroid preparations with lower systemic bioavailability, such as BDP and budesonide, have been studied. Topical BDP was found in small open trials to be as effective as betamethasone [18, 24] and PP enemas [25, 26] for active distal ulcerative colitis, with less adrenal suppression. However, a small double-blind trial found 1 mg BDP enemas to be less effective than 30 mg PP enemas.[26] The difference between the findings of this latter study and our results may be explained by the higher dose of BDP we used, and by the greater number of patients treated. More recently, the efficacy of BDP enemas has been confirmed by a Dutch study, in which the combination of BDP 3 mg enema and 5-ASA 1 g enema was significantly better than the single agents.[27]

The results of our multicentre study confirm that BDP 3 mg enemas are as efficacious as PP 30 mg enemas in distal active ulcerative colitis, without interference with the hypothalamic–pituitary–adrenal axis function.

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