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Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study

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SUMMARY

Aim: To evaluate efficacy and safety of oral beclometasone dipropionate (BDP) when added to 5-ASA in the treatment of patients with active ulcerative colitis.

Methods: In a 4-week, placebo-controlled, double-blind study, patients with extensive or left-sided mild to moderate active ulcerative colitis were randomized to receive oral 5-ASA (3.2 g/day) plus BDP (5 mg/day) or placebo. Clinical, endoscopic and histologic features, and haematochemical parameters were recorded at baseline and at the end of the study.

Results: One hundred and nineteen patients were enrolled and randomly treated with BDP plus 5-ASA ($n = 58$) or placebo plus 5-ASA ($n = 61$). Both treatment groups showed a statistically significant decrease of disease activity index (DAI) and histology score at the end of treatment ($P = 0.001$, each). DAI score was lower in the BDP group than in the placebo group ($P = 0.014$), with more patients in clinical remission in the BDP group (58.6% vs. 34.4%, $P = 0.008$). Serum cortisol levels significantly decreased in BDP group vs. baseline ($P = 0.002$), but without signs of pituitary-adrenal function depletion. A low incidence of adverse events was observed in both groups.

Conclusions: Oral BDP in combination with oral 5-ASA is significantly more effective than 5-ASA alone in the treatment of patients with extensive or left-sided active ulcerative colitis.

INTRODUCTION

Glucocorticosteroids (GCS) therapy is a well established approach for active ulcerative colitis,[1, 2] but their prolonged use is limited by the risk of systemic steroid-related adverse effects.[3] In recent years, greater efforts have been spent to develop a new family of GCS with the same efficacy as traditional GCS, but with a more favourable safety profile. Beclometasone dipropionate (BDP) displays a prompt and potent topical anti-inflammatory activity, but its systemic activity is limited.[4] BDP has the advantage of reducing systemic side-effects, such as Cushing-like syndrome and sup-

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pression of the hypothalamic–pituitary–adrenal axis, which are evident with conventional corticosteroid treatment.[5, 6] The reduction in side-effects following topical delivery of BDP is largely due to the high degree of first pass metabolism following absorption from the lower gastrointestinal tract.[7] The efficacy of rectally administered BDP is well demonstrated and comparable to that of conventional GCS[8–10] or aminosalicylates.[11, 12]

Recently, an oral controlled-release preparation of BDP (Clipper tablets; Chiesi Farmaceutici S.p.A., Italy) has been developed with an acid-resistant methacrylate film coating (Eudragit L100/55) that prevents the tablets from dissolving in the stomach and a modified release core of hydroxypropyl methylcellulose (Methocel K4M) that dissolves at pH values lower than 6.0, so the drug is released in the distal small bowel and during the passage throughout the colon.[13] Compared with the two different pH dependent formulations of oral budesonide, the other recently launched GCS with low systemic bioavailability, oral BDP, could be considered similar to the controlled ileal release formulation for the treatment of active ileocaecal Crohn's disease, in which the drug is released at a pH above 5.5 and 50–80% of an oral dose is absorbed in the ileum and proximal colon.[14] In this other formulation, budesonide is released from an Eudragit coating when pH exceeds 6.4. In this context it appears relatively ineffective in patients with active Crohn's disease confined to the left colon and rectum[15] in whom colonic pH may be low.[16] BDP plasma concentrations following the oral administration of a 5-mg tablet[13] and also following single oral dosing and two single rectal administrations (enemas and suppositories) were found to be very low.[17] In patients who had undergone terminal ileostomy, a single oral administration of BDP 5 mg tablet was followed by the presence of BDP and its major metabolite (beclometasone 17-monopropionate) in ileostomy effluents, supporting a significant release of BDP at the site of action.[18] The therapeutic efficacy of oral BDP in the treatment of active ulcerative colitis appears to be comparable to that of 5-ASA, as demonstrated in previous studies.[19, 20]

The present study was performed to compare efficacy and safety of oral BDP with placebo as adjunctive therapy to oral 5-ASA in the treatment of active ulcerative colitis.

MATERIALS AND METHODS

Patients

Out-patients of both sexes, aged at least 18 years, with a definite diagnosis of extensive or left-sided active ulcerative colitis were eligible for inclusion. At entry patients had a disease activity index (DAI) score ranging from 3 to 10 points. DAI is a 12-point scoring system that includes endoscopic and clinical parameters (Table 1).[21] Patients with a DAI score < 3 were considered in clinical remission, 3–6 with mild, 7–10 moderate, and >10 severe activity of the disease.

Patients with a new diagnosis of ulcerative colitis, severe ulcerative colitis or in clinical remission on the basis of DAI score were excluded from the study. Other exclusion criteria included severe renal or hepatic failure, diabetes mellitus, gastroduodenal disease, heart failure, severe or moderate hypertension, neoplastic disease, psychosis, alcohol and drug abuse, pregnancy or lactation. Patients receiving corticosteroid treatment for a period of 1 month prior to study initiation or 5-ASA at a dosage > 3.2 g/day or sulfasalazine at a dosage > 2 g/day for 2 weeks preceding study entry and during the trial were also excluded.

Table 1. Disease activity index (DAI), a qualitative rating scale with four subscales

	Score
Stool frequency (daily average)	
Normal	0
1–2 stools/day > normal	1
3–4 stools/day > normal	2
> 4 stools/day > normal	3
Rectal bleeding	
None	0
Streaks of blood	1
Obvious blood	2
Mostly blood	3
Mucosal appearance	
Normal	0
Mild friability	1
Moderate friability	2
Exudation, spontaneous bleeding	3
Physician's rating of disease activity	
Normal	0
Mild	1
Moderate	2
Severe	3

Maximum score = 12.

The study was conducted according to the Declaration of Helsinki and was ap proved by local Ethics Committees. Written informed consent was obtained from each patient prior to study initiation.

Study drugs

BDP, the corresponding placebo and a commercially available preparation of 5-ASA (Asacol 400 mg tablets; Bracco Industria Chimica, Italy) were supplied by Chiesi Farmaceutici S.p.A. (Parma, Italy). BDP 5 mg tablets and placebo tablets were identical in appearance and were provided in identical glass bottles. Patients were randomly assigned to receive one tablet of BDP 5 mg or one tablet of placebo administered once daily early in the morning (8–9 AM). Eight tablets per day of 5-ASA 400 mg were also administered to both treatment groups for the whole study period.

Methods and assessment of the treatment results

The study was conducted according to a randomized, double-blind, placebo-controlled design. At each participating centre, treatment allocation was made from blocks of four numbers produced by a computer-generated randomization list (SAS programme, version 6.12). The patients were treated for 4 weeks and compliance was checked by counting residual study medication at the end of the treatment period. Patients were considered compliant if they had taken at least 75% of the medication.

A screening visit (visit 1) was planned between a maximum of 15 days and a minimum of 3 days before entry to assess eligibility and to register clinical symptoms of patients (number of movements, quality of life, presence of blood in the stools) and to obtain written informed consent. To determine activity and extent of the disease, all eligible patients were graded with clinical findings and underwent a pancolonoscopy at baseline (visit 2) and after 4 weeks of treatment (visit 4). Endoscopic activity was graded according to Baron's criteria.[22] A clinical control was performed after the first 2 weeks of treatment (visit 3) when the study medication for the next 2 weeks of treatment was also assigned. At the end of the treatment period, patients were classified as 'responders' if their DAI score was reduced by at least 3 points compared to baseline.[23]

To establish the histologic activity of ulcerative colitis, mucosal biopsy specimens were obtained from each segment of the colon (ascending, transverse, descending and sigmoid) and rectum, and always from the most severely affected area in each segment. The degree of inflammation in the histological specimens was graded according to Truelove & Richard's criteria.[24]

The primary outcome measures for efficacy were daily stool frequency, blood in stools, subjective sense of well-being, and mucosal appearance at colonoscopy. Secondary efficacy outcome measures were histology and erythrocyte sedimentation rate (ESR).

Blood chemistry tests (haematological, liver and renal function tests, plasma glucose, electrolytes) were performed on all patients at baseline and at the end of the treatment. Blood pressure, heart rate and weight were monitored at baseline and after 4 weeks. Adverse events were recorded throughout the study period.

The primary outcome measure for safety was the effect of oral BDP on endogenous cortisol production, which was assessed by measuring morning serum cortisol levels and by monitoring of signs of pituitary-adrenal function (leg oedema, Cushing-like syndrome, hypertension, diabetes). Plasma samples were drawn at 08.00–10.00 hours, following an overnight fast (normal range 5–25 $\mu g/dL$).[25] Samples were frozen at -20 °C and evaluated in a centralized independent laboratory for the determination of serum cortisol levels. A high-performance liquid chromatography method was used.

Statistical analysis

The sample size was calculated on the assumption that 65% of patients would respond to BDP treatment and 40% would respond to placebo. Sixty-two patients were assigned to each treatment group when a two-tailed test was employed with $\alpha = 0.05$ and $1\text{-}\beta = 0.80$.

Student's *t*-test and Wilcoxon's rank sum test were used to compare the two treatment groups at baseline. The intention-to-treat (ITT) population included all recruited patients with any evidence of having received at least one dose of study medication. The last observation carried forward (LOCF) method was applied to deal with missing data.

The Wilcoxon Signed rank test was performed to compare the changes from baseline of the efficacy variables in the within treatment analysis, while the Wilcoxon rank sum test was used to verify the differences between the two groups.

Table 2. Demography and disease history in BDP group and in placebo group at study entry

	BDP (n = 58)	Placebo (n = 61)
Age (year)*	43.1 (14.5)	44.7 (13.1)
Weight (kg)*	68.1 (12.2)	70.4 (12.2)
Height (cm)*	168.6 (7.9)	168.3 (8.5)
Male	41 (71)	43 (70)
Smoker	5 (9)	6 (10)
Alcohol consumption	12 (21)	12 (20)
Coffee consumption	31 (53)	32 (52)
Diagnosis		
Left ulcerative colitis	38 (66)	47 (77)
Pancolitis	20 (34)	14 (23)
5-ASA daily dosage before study entry (g)*	1.72 (0.71)	1.78 (0.79)
Disease activity (DAI score)		
Mild	14 (24)	12 (20)
Moderate	44 (76)	49 (80)
SBP (mmHg)*	127 (11)	124 (11)
DBP (mmHg)*	77 (6)	76 (7)
Heart rate (bpm)*	78 (8)	77 (8)

Data are n (%) unless otherwise indicated; * mean (s.d.).
DAI = disease activity index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Changes in laboratory values were analysed using the t-test for paired data. The incidence of adverse events was compared using the Chi-squared or the Fischer's exact test.

RESULTS

One hundred and nineteen patients were enrolled in 11 Italian centres. A further five patients were not recruited because of the end of the enrolment period.

Table 3. Disease activity index in BDP group (n = 58) and in placebo group (n = 61) at baseline and after 4 weeks of treatment

	Baseline	4 weeks	P
BDP + 5-ASA	6.3 (1.9)	2.6 (2.6)*	0.001
Placebo + 5-ASA	6.4 (1.5)	3.4 (2.2)*	0.001

Data expressed as a mean (s.d.); * P = 0.014 between treatments.

Patient characteristics of the two treatment groups at study entry were similar for demographic parameters, smoking habits, extent, severity and duration of the disease, and the mean 5-ASA daily dosage administered before entry (Table 2).

Fourteen patients (11.8%) did not complete the study: two (1.7%) in the BDP group (one for clinical worsening and one due to an adverse event) and 12 (10.1%) in the placebo group (nine because of clinical worsening and three due to adverse events) (Figure 1). No patient was considered non-compliant.

Efficacy of oral BDP on colitis

ITT analysis demonstrated that both treatment groups reached a significant reduction (P = 0.001) in the DAI score, with a significant difference (P = 0.014) in favour of the BDP group compared to the placebo group (Table 3).

The percentage of patients in clinical remission was higher in the BDP group (58.6%, n = 34) compared to the placebo group (34.4%, n = 21) and the difference between the two groups was statistically significant (P = 0.021) (Figure 2). Only one patient in the BDP

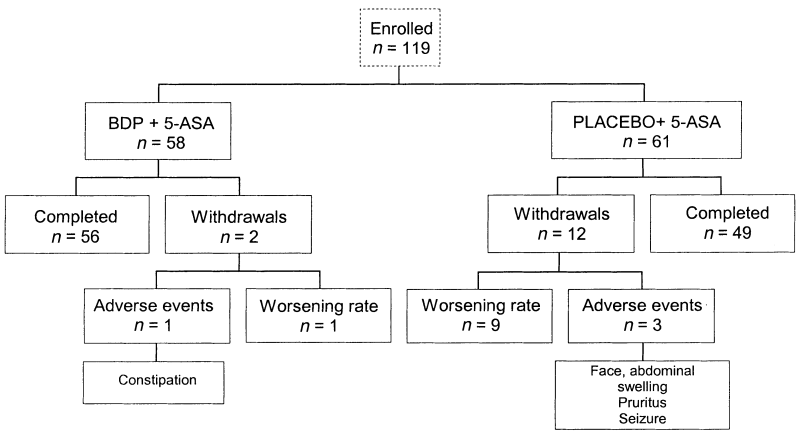

Figure 1. Disposition of patients. Chi-squared: P = 0.021 between treatments.

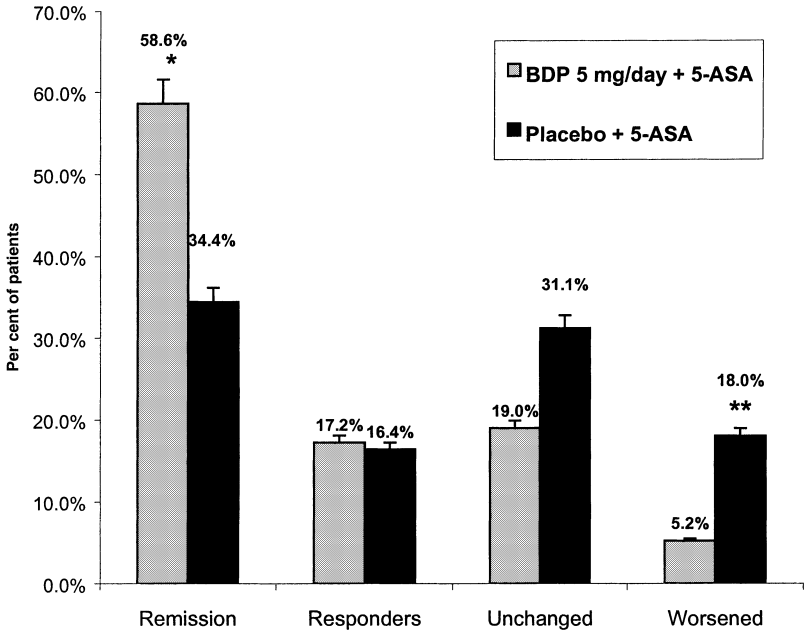

Figure 2. Disease activity index (DAI) evaluation in the BDP group ($n = 58$) and in the placebo group ($n = 61$) at baseline and after 4 weeks of treatment.

Table 4. Disease activity index variables at baseline and after 4 weeks of treatment in the BDP group ($n = 58$) and in the placebo group ($n = 61$)

	Baseline	4 weeks	P
BDP + 5-ASA			
Stool frequency	2.0 (0.8)	0.8 (1.0)	0.001
Rectal bleeding	1.5 (0.8)	0.4 (0.6)*	0.001
Sense of well-being	1.0 (0.7)	0.4 (0.6)**	0.001
Colonoscopy	1.8 (0.5)	1.0 (0.9)	0.001
Placebo + 5-ASA			
Stool frequency	2.0 (0.7)	1.0 (0.9)	0.001
Rectal bleeding	1.5 (0.7)	0.6 (0.7)	0.001
Sense of well-being	1.0 (0.6)	0.7 (0.5)	
Colonoscopy	2.0 (0.5)	1.1 (0.8)	0.001

Data expressed as a mean (s.d.); score 0–3; * $P = 0.017$ between treatments; ** $P = 0.005$ between treatments.

group, but nine patients in the placebo group withdrew from the study due to treatment inefficacy ($P = 0.01$ between treatments).

The DAI variables were also singularly evaluated (Table 4) and a more significant improvement in rectal bleeding and sense of well-being was noted in the BDP group compared to the placebo group ($P = 0.017$ and $P = 0.005$, respectively).

The endoscopic score was reduced in both groups after 4 weeks: a normalization of intestinal mucosa was observed in 18 out of 58 (31%) patients in the BDP group and 10 out of 61 (16%) patients in the placebo group. Histological assessment showed a significant improvement vs. baseline in both groups ($P = 0.001$, each). No significant difference in the between treatment analysis was observed.

Reflecting an improvement in inflammatory status, mean ESR vs. baseline was significantly reduced in the BDP group (from 19.2 ± 15.2 to 14.2 ± 13.1, $P = 0.001$) and not in the placebo group (from 17.8 ± 13.3 to 18.6 ± 17.6), with a significant difference between treatments ($P = 0.05$) at the end of the study period. In comparison with the placebo group a significant increase of erythrocytes ($P = 0.015$, $P = 0.049$ between treatments), haemoglobin ($P = 0.001$, $P = 0.001$ between treatments) and haematocrit ($P = 0.001$, $P = 0.001$ between treatments) was also observed in the BDP group, in line with the reduced rectal bleeding.

Safety results and effect on adrenal function

No changes in blood pressure, heart rate and weight were detected in either treatment groups at the end of the treatment period. There were no modifications in blood chemistry, liver and renal function tests and electrolytes. A slight but significant decrease of plasma glucose from 88.9 to 84.2 mg/dL ($P = 0.004$) and of platelet count from 276.3 to 262.3 10^9/L ($P = 0.036$) was observed.

Mean morning serum cortisol levels were assessed in 53 out of 58 patients in the BDP group and in 51 out of 61 patients in the placebo group, they were significantly decreased in the BDP group at the end of the treatment period ($P = 0.002$), but were still within the normal range. Four out of 53 BDP-treated patients (7.5%) showed levels less than the lower reference limit of 5 μg/dL, but no signs of pituitary-adrenal function depletion, such as leg oedema or Cushing-like syndrome were observed.

Adverse events

Two out of 58 (3.4%) patients in the BDP group and four out of 61 (6.5%) in the placebo group experienced adverse events. None of the adverse events recorded was serious and treatment was suspended in one patient in the BDP group (constipation) and three patients in the placebo group (facial and abdominal swelling, seizures, pruritus). The adverse events recorded were defined as doubtfully related to the test treatments.

DISCUSSION

Previous studies have demonstrated that BDP administered as controlled-release tablets produces a positive response in patients with active mild to moderately severe ulcerative colitis[19] and is as effective as oral 5-ASA.[20] Many ulcerative colitis patients experience relapses not always successfully treated with oral 5-ASA alone. In these patients, in order to reduce the mucosal inflammation and to improve the quality of life, it is useful to add systemic or local corticosteroid therapy.[26] Its limited systemic activity means that BDP has the advantage of reduced systemic side-effects such as suppression of the hypothalamic–pituitary–adrenal axis and Cushing-like syndrome, which are evident with conventional GCS. The two treatment groups were well balanced for demographic parameters, severity and duration of the disease, and the 5-ASA daily dosage taken before study entry. Considering the lack of universally accepted efficacy parameters in ulcerative colitis trials, the widely employed DAI of Sutherland *et al.*[21] was used as the main outcome evaluation. The duration of treatment (4 weeks) is considered to be sufficient for therapeutic response in patients with active disease.[27]

Due to the high 5-ASA dosage (3.2 g/day) administered in all included patients throughout the study period, even in placebo-treated patients, we observed an improved inflammatory status in the colon and rectum, which translated into a significantly decreased DAI score ($P < 0.001$) vs. baseline.

As adjunctive therapy to oral 5-ASA, however, oral BDP has been found to significantly improve clinical symptoms and mucosal appearance in patients with active ulcerative colitis. After a 4-week treatment period, a significant improvement in the disease activity associated with a higher percentage of patients in clinical remission in the BDP group (58.6% compared with 34.4% in the placebo group) was achieved. In favour of the BDP group there was also a significant difference between treatments with regard to the number of withdrawn patients due to the treatment inefficacy. The significant reduction of ESR and rectal bleeding in BDP-treated patients also confirmed the positive response of the inflammatory process. Decreased loss of blood in stools reflected a significant increase in erythrocytes count, haemoglobin and haematocrit. The histopathologic scores were significantly reduced compared with baseline in both treatment groups.

Even in combination with oral 5-ASA, the good safety profile of oral BDP shown in previous studies has been confirmed.[19, 20] Although there was a significant reduction in serum cortisol levels at the end of treatment, the mean value remained within the normal range, and, even though four patients had serum cortisol levels below the lower reference limit, no clinical signs or adverse reactions related to adrenal depletion were recorded. Also the incidence of adverse events was low, with no serious side-effects recorded.

In conclusion, oral BDP controlled-release formulation at a dosage of 5 mg/day, as adjunctive therapy to 5-ASA, was found to be significantly more efficacious compared with oral 5-ASA alone in the treatment of mild to moderately severe active ulcerative colitis, and is generally well tolerated without inhibitory effects on endogenous serum cortisol. Due to the good safety profile shown by oral BDP in the 4-week treatment of active ulcerative colitis, further studies to assess the efficacy and interference with hypothalamic–pituitary–adrenal function, when long-term use is proposed, will be an important area for investigation.

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