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Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study

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SUMMARY

Aim: To explore the efficacy and safety of the topically acting steroid beclometasone dipropionate (BDP) in an oral controlled release formulation in the treatment of extensive or left-sided ulcerative colitis.

Methods: In a multicentre, randomised, parallel-group, single-blind study, patients with active mild to moderate ulcerative colitis were randomised to a 4-week treatment with BDP 5 mg/day o.d. vs. 5-ASA 0.8 g t.d.s. The primary efficacy variable was the decrease of Disease Activity Index (DAI) (clinical symptoms and endoscopic appearance of mucosa). Safety was evaluated by monitoring adverse events, vital signs, haematochemical parameters and adrenal function.

Results: One hundred and seventy-seven patients were enrolled and randomly treated with BDP ($n = 90$) or 5-ASA ($n = 87$). Mean DAI score decreased in both treatments groups ($P < 0.0001$ vs. baseline for both groups). Clinical remission was achieved in 63.0% of patients in the BDP group vs. 62.5% in the 5-ASA group. A significant DAI score improvement ($P < 0.05$) in favour of BDP was observed in patients with extensive disease. Both treatments were well tolerated. Mean plasma cortisol levels were significantly reduced vs. baseline in BDP recipients, but without signs of pituitary–adrenal function depletion.

Conclusion: Oral BDP gave an overall treatment result in patients with active ulcerative colitis without signs of systemic side-effects.

INTRODUCTION

Approximately 95% of all incident cases of ulcerative colitis are mild or moderate in severity, and most patients have an endoscopic involvement distal to the splenic flexure,[1] although proximal extension is not uncommon and should be considered if the clinical pattern worsens.[2] The aminosalicylic acid derivatives of sulfasalazine have a fundamental role in the treatment of mild or moderate ulcerative colitis, and oral formulations are effective for both proximal and distal colitis.[3, 4]

Corticosteroids (CS) have been widely used for the treatment of inflammatory bowel diseases for over 40 years because of their potent anti-inflammatory

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activity and their interference with immunological responses,[5, 6] but the therapeutic benefits are compromised by an extensive spectrum of side-effects and a negative impact on quality of life. For this reason, the past decade was characterised by the introduction of topically acting corticosteroids with a more favourable safety profile, such as tixocortol pivalate, budesonide and beclometasone dipropionate (BDP). These topically acting corticosteroids are characterised by a prompt and potent anti-inflammatory activity and a low systemic bioavailability, which is mainly achieved through an extensive first-pass metabolism.[7] These newer compounds provide advantages over the older systemic corticosteroids by minimising the occurrence of the adverse effects typical of this drug class, whilst achieving equivalent, or even superior efficacy.[8]

At first developed for the treatment of asthma and allergic rhinitis, BDP has been formulated into rectal suspension enema and more recently into oral delayed-release preparations for the treatment of patients with ulcerative colitis. The rectal formulation of BDP has been found to be beneficial in the treatment of active distal ulcerative colitis, with an efficacy comparable to that of conventional corticosteroids or aminosalicylates, from the results of controlled studies vs. hydrocortisone, prednisolone or betamethasone phosphate[9–13] and comparative studies vs. mesalazine (5-aminosalicylic acid; 5-ASA).[14, 15]

The oral controlled release formulation of BDP is constituted by a gastro-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. In this way the drug is released in the distal small bowel and throughout the passage of the colon, as demonstrated by *in vivo* gamma scintigraphy technique to evaluate gastrointestinal transit and release of oral BDP.[16] Oral BDP could be considered similar to the controlled ileal release formulation of recently launched Budesonide 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.[17]

The aim of the present study was to explore the efficacy and safety of oral BDP in the treatment of extensive or left-sided acute symptomatic ulcerative colitis and compare it with an established treatment such as oral delayed-release 5-ASA.

METHODS

Patients

The main criterion for inclusion was a definite diagnosis of extensive or left-sided mild to moderately active ulcerative colitis. Out-patients of either sex, aged 18–70 years, who satisfied these criteria and had a Disease Activity Index (DAI) score > 3 and < 10 were eligible for enrolment.[18] DAI is a 12-point scoring system which includes clinical (stool frequency, rectal bleeding and physician's assessment of disease severity) and endoscopic (mucosal appearance) parameters (Table 1). Patients with a DAI score < 3 were considered in clinical remission, 3–6 in mild, 7–10 in moderate, and > 10 in severe activity of the disease.[19]

Exclusion criteria were: severe ulcerative colitis or clinical remission on the basis of DAI score, severe renal, liver or heart failure, diabetes mellitus, active gastroduodenal ulcer, osteoporosis, severe or moderate hypertension, neoplastic disease, psychotic disorders, drug or substance abuse disorder, known hypersensitivity to corticosteroids or aminosalicylates, pregnancy and lactation. Patients undergoing treatment with corticosteroid medications, 5-ASA or sulfasalazine for at least one

Table 1. Disease Activity Index (DAI)

	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.

month prior to enrolment were excluded, and the use of these agents as concomitant treatments during the study period was not allowed. In case of bacterial or viral infections, other than those affecting the gastrointestinal tract, treatment with antibacterial drugs was allowed, as well as long-standing therapies for concomitant diseases unrelated to ulcerative colitis (i.e. hypertension).

This study was conducted in accordance with the Declaration of Helsinki and was approved by local Ethic Committees. All patients provided written informed consent before entry.

Study drugs

Chiesi Farmaceutici S.p.A. (Parma, Italy) supplied both BDP 5 mg tablets and 5-ASA 400 mg tablets (Asacol 400 mg tablets; Bracco S.p.A., Italy). Patients were randomly assigned to receive one tablet of BDP 5 mg/day (once daily early in the morning) or six tablets of 5-ASA 400 mg per day (two tablets early in the morning, two tablets at lunchtime and two tablets in the evening) for 4 weeks.

Study design

This study was performed according to a multicentre, single blind, randomised and controlled design. Due to the technical difficulties of performing a study with a double-blind, double-dummy design, the third-part blind observer method was used to assess the efficacy of the test treatments. In order to ensure unbiased efficacy assessments, the investigators who performed endoscopic and histological examinations and the evaluation of the clinical symptoms of ulcerative colitis were blinded to patients' treatment assignment, whereas the investigators in charge of treatment allocation were excluded from all efficacy assessments.

At each participating centre, treatment allocation was made from blocks of four numbers produced by a computer-generated randomisation list (SAS software, version 6.08). The investigators who had assigned the test treatments checked compliance at each visit by counting residual study medication.

Experimental procedures

During the screening visit (Visit 1), the eligible patients provided a written informed consent. The medical history of each one was collected, and a complete clinical evaluation to determine vital signs (heart rate, systolic and diastolic blood pressure), body weight and clinical parameters of ulcerative colitis (stool frequency, blood in stools, general health conditions) was performed.

All patients were graded with clinical findings and underwent to a pancolonoscopy to determine activity and extension of the disease and to obtain tissue for histopathology during the baseline visit (5–10 days after the screening visit, Visit 2) and at the end of the 4-week treatment period (Visit 4). Endoscopic activity was graded according to Baron's criteria.[20] Mucosal biopsy specimens were obtained from each segment of the colon (ascending, transverse, descending and sigmoid) and rectum to establish the histologic activity of ulcerative colitis. The degree of inflammation in the histological specimens was graded according to the criteria of Truelove and Richard.[21] A complete haematochemical evaluation, including erythrocyte count (RBC), white blood cell count (WBC), platelet count, urea nitrogen, plasma glucose, creatinine, alanine aminotransferase, aspartate aminotransferase, sodium, potassium, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total and fractionated serum proteins and plasma cortisol, was carried out in each patient at baseline and at the end of the treatment period. All the included patients returned also after 2 weeks (Visit 3) for a complete clinical control, for a compliance check and to receive study medication for the next 2 weeks of treatment. During this visit an endoscopic evaluation could be performed if thought necessary by the investigators. Adverse events were recorded throughout the study period. Blood pressure (BP), heart rate (HR) and body weight were monitored at each visit. The variation of DAI according to Sutherland *et al.* from Visit 2 to Visit 4 was used as primary efficacy parameter[18] (Table 1). The clinical improvement was defined as a reduction of at least three points in the DAI score from baseline values (patients 'responders').[22]

Clinical symptoms of ulcerative colitis other than those included in the DAI (stool consistency, abdominal pain, tenesmus and the presence of mucus in stools) (Table 2) and haematochemical indices of inflammation (ESR, WBC and CRP) were considered as secondary efficacy parameters.

The primary safety parameter was the effect of oral BDP on endogenous cortisol production, which was evaluated by measuring morning plasma cortisol levels

Table 2. Secondary efficacy variables

Score	
Stool consistency	
Normal	0
Partially formed	1
Semi-liquid	2
Liquid	3
Abdominal pain	
Normal	0
Mild	1
Moderate	2
Severe	3
Tenesmus	
Normal	0
Mild	1
Moderate	2
Severe	3
Mucus in stools	
None	0
Streaks	1
Obvious	2
Mostly	3

and by the monitoring of signs of pituitary–adrenal function depletion (leg oedema, Cushing-like syndrome, hypertension, diabetes). Plasma samples were drawn at 08.00–10.00 a.m. following an overnight fast (normal range 5–25 μg/dL).[23]

Statistical analysis

The sample size calculation was based on the hypothesis that after treatment 80% of patients in the BDP group would be in remission (a DAI score < 3), compared with 60% in the 5-ASA group. With a two-tailed test of $\alpha = 0.05$ and $1-\beta = 0.80$, two groups of 80 patients each were required. Student's *t*-test and the Wilcoxon two-sample test were used to compare the two treatment groups at baseline. The Wilcoxon signed-rank test was used to compare efficacy outcome measures of the two groups during the treatment, and the Wilcoxon two-sample test was used to compare the between-group changes from baseline to day 28. The distribution of patients 'in remission' and 'improved' in the two treatment groups was compared using the chi-square test.

All the analyses were conducted on an intention-to-treat (ITT) basis, and efficacy and safety analyses were performed on all patients who had received at least one dose of study medication and who had attended at least one visit after baseline. Haematochemical and adrenal function parameters were analysed using Student's *t*-test for paired data and non-paired data within and between treatments, respectively. As well as the randomisation list, the statistical analysis was performed with SAS software, version 6.08. Data are expressed as mean ± standard error of the mean (s.e.m.), except when indicated.

RESULTS

A total of 177 patients (90 in the BDP group and 87 in the 5-ASA group) were randomised to treatment in 13 Italian centres. The groups did not significantly differ for baseline demographics and disease duration, even if, despite randomisation, patients with a significantly higher mean DAI (6.07 vs. 5.31; $P < 0.05$) were enrolled in the BDP arm (Table 3). The majority of ulcerative colitis patients suffered from left-sided disease extending 25–50 cm (71.8%). However, compared with the 5-ASA group, the BDP group had a significantly higher percentage of patients with extensive ulcerative

Table 3. Patients' characteristics

Variables	BDP 5 mg/day $n = 90$	5-ASA 2.4 g/day $n = 87$	*P*-value
Sex (M/F), *n*	57/33	50/37	n.s.
Age (years)	41.1 (1.6)	45.4 (1.5)	n.s.
Body weight (kg)	66.6 (1.6)	69.0 (1.2)	n.s.
Duration of disease (years)	5.3 (0.5)	5.4 (0.7)	n.s.
Patients with left-sided ulcerative colitis, *n* (%)	58 (64.4)	69 (79.3)	n.s.
Patients with extensive ulcerative colitis, *n* (%)	32 (35.6)	18 (20.7)	< 0.05
DAI	6.06 (0.20)	5.30 (0.18)	< 0.05

Data expressed as a mean (s.e.m.) except when indicated.

colitis (transverse colon or pancolitis) (35.6% vs. 20.7%; $P < 0.05$) (Table 3). Even though the study was powered for the analysis of all patients, due to the size of the study subjects with extensive or left-sided forms were identified *post hoc* for a further investigation.

Twenty-five patients (14.1%) did not complete the study: 18 (20%) in the BDP group (eight patients were lost to follow-up, four patients were non-compliant, four patients had an insufficient therapeutic response, one patient committed a protocol deviation and one patient experienced an adverse event) and seven (8%) in the 5-ASA group (three patients were non-compliant, two patients were lost to follow-up, one patient had an insufficient therapeutic response and one patient experienced a concomitant disease) (Figure 1). The relevant number of patients lost to follow-up could have been due both to an attempt to conduct the study in many centres and the inclusion of out-patients which, especially in the case of mild severity of the disease with fast remission of symptoms, did not return for the following visits.

During the study, only one patient (in the 5-ASA group) received antibacterial therapy (ampicillin 2 g/day p.o. for 7 days for influenza treatment).

Efficacy evaluation

One hundred and fifty-two patients (72 in the BDP group and 80 in the 5-ASA group) completed the treatment period (Figure 1). According to ITT analysis, the primary efficacy variable DAI was evaluated in 73 patients in the BDP group and 80 patients in the 5-ASA group: one patient in each group completed the treatment period, but refused to be submitted to other endoscopic controls after the baseline visit, and two patients in the BDP group and one patient in the 5-ASA group underwent pancolonoscopy after 2 weeks of treatment at Visit 3, but they later withdrew from the study because of insufficient therapeutic response.

At the final visit the mean DAI score was significantly reduced from baseline in both treatment groups: from 6.10 ± 0.20 (median 6, range 3–10) at baseline to 2.44 ± 0.29 (median 2, range 0–11) after treatment in the BDP group, and from 5.29 ± 0.17 (median 5, range 2–9) to 2.03 ± 0.23 (median 1, range 0–9) in the 5-ASA group (both $P < 0.0001$ vs. baseline). These results were also confirmed by the significant improvement starting from the 2-week visit (Visit 3) in both treatment groups of the single clinical and endoscopic findings included in the DAI score (stool frequency, rectal bleeding, physician's rating of disease activity and endoscopic appearance of mucosa) [all $P < 0.0001$ vs. baseline, except for the physician's assessment ($P < 0.01$ at Visit 3 in both treatment groups)], and also of the secondary efficacy clinical variables (stool consistency, abdominal pain, tenesmus and mucus in stools) (all $P < 0.0001$ vs. baseline).

The histological assessment confirmed the clinical and endoscopic findings, with the mean score of Truelove and Richard decreasing from 1.76 at baseline to 0.93 after treatment in the BDP group, and from 1.62 to 0.90 in the 5-ASA group ($P < 0.001$ vs. baseline in both groups). Twenty-three of 70 (32.9%) patients in the BDP group and 27/77 (35.1%) patients in the 5-ASA

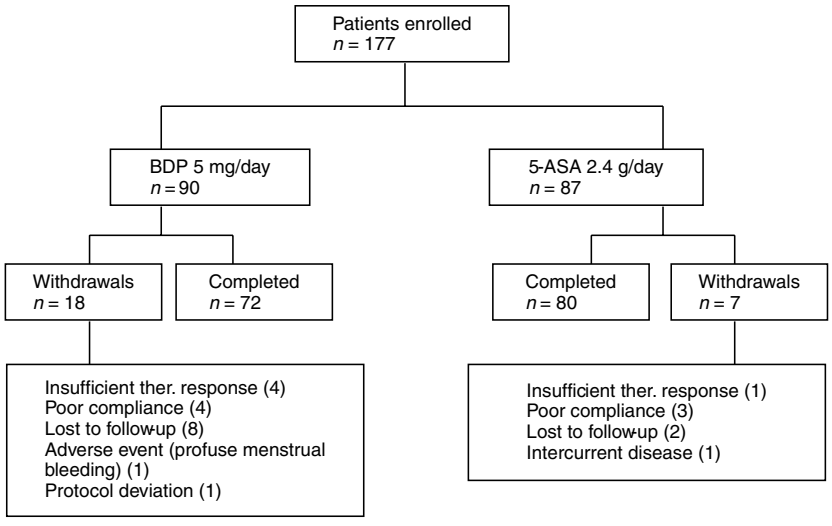

Figure 1. Trial profile.

group showed histological remission. ESR decreased significantly from baseline in both groups (from 19.5 ± 1.68 to 15.3 ± 1.62, $P < 0.05$ in the BDP group and from 18.0 ± 1.63 to 13.8 ± 1.25, $P < 0.01$), reflecting an improvement of the inflammatory status. No post-treatment changes in WBC or CRP protein were observed.

The percentages of patients in clinical remission and with a significant clinical improvement did not significantly differ between the two treatment groups, even when extensive or left-sided colitis were independently considered (P = n.s. in each case) (Figures 2 and 3).

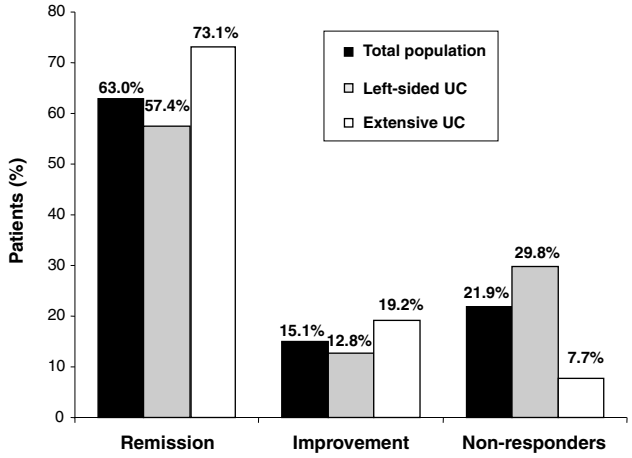

Figure 2. Percentage of responders in the BDP group: total population ($n = 73$), left-sided ulcerative colitis ($n = 47$), extensive ulcerative colitis ($n = 26$).

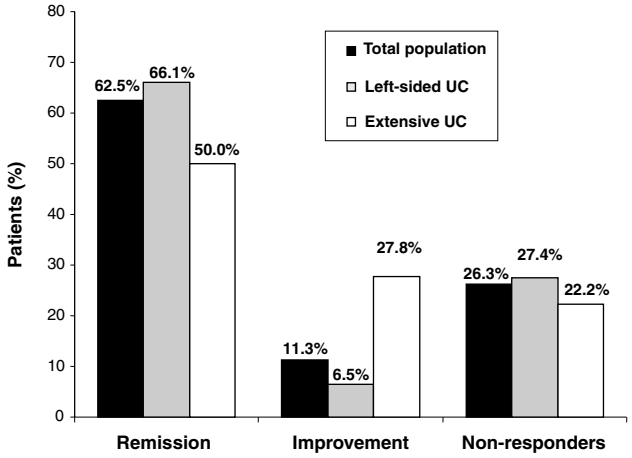

Figure 3. Percentage of responders in the 5-ASA group: total population ($n = 80$), left-sided ulcerative colitis ($n = 62$), extensive ulcerative colitis ($n = 18$).

The results of this study also suggest that patients with extensive disease were more likely to obtain a better clinical improvement with BDP compared to 5-ASA. A significant reduction of the mean DAI score was achieved in both groups: from 6.50 ± 0.27 (median 7, range 4–10) to 2.15 ± 0.42 (median 2, range 0–8) in the BDP group and from 5.78 ± 0.41 (median 6, range 2–8) to 2.67 ± 0.55 (median 2.50, range 0–8) in the 5-ASA group, $P < 0.0001$), with a significantly lower mean final DAI score in the BDP group ($P < 0.05$) (Figure 3). Moreover, patients suffering from left-sided ulcerative colitis obtained a significant clinical improvement in both treatment groups ($P < 0.0001$) at the end of study period, with no difference in the final

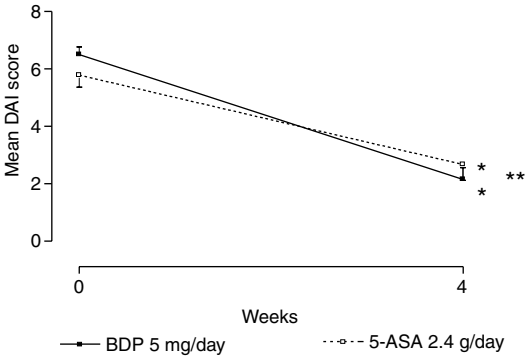

Figure 4. Disease Activity Index (DAI) in patients with extensive ulcerative colitis in the BDP group ($n = 26$) and in the 5-ASA group ($n = 18$). Data expressed as mean ± s.e.m. *$P < 0.0001$ vs. baseline. **$P < 0.05$ between treatments.

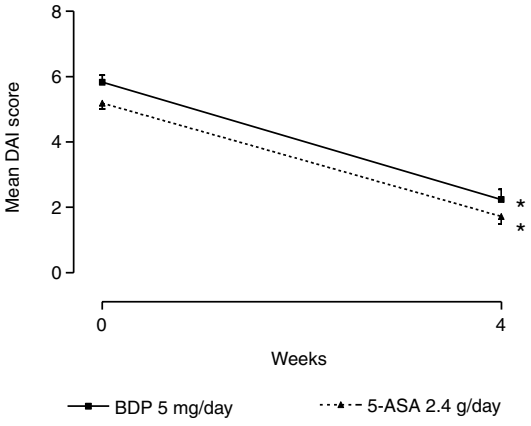

Figure 5. Disease Activity Index (DAI) in patients with left-sided ulcerative colitis in the BDP group ($n = 47$) and in the 5-ASA group ($n = 62$). Data expressed as mean ± s.e.m. *$P < 0.0001$ vs. baseline.

DAI score between groups (Figures 4 and 5), and with median values which decreased from 6 (range 3–10) to 2 (range 0–8) in the BDP group and from 5 (range 2–9) to 1 (range 0–6) in the 5-ASA group.

The single clinical and endoscopic parameters of the DAI score (stool frequency, rectal bleeding, physician's rating of disease activity and mucosal appearance) and the secondary efficacy clinical variables (stool consistency, abdominal pain, tenesmus and mucus in stools) were also separately analysed for extensive and left-sided subgroups, as shown in Table 4 and Table 5. In extensive forms, the presence of mucus in stools was not significantly reduced in the 5-ASA group, while all the other clinical and endoscopic primary and secondary parameters were statistically improved in both arms at the end of the study period. The improvement of stool frequency and consistency, rectal bleeding and abdominal pain started from the 2-week visit (Visit 3) in both groups, while presence of mucus in stools in the BDP group, tenesmus in the 5-ASA group and physician's assessment of disease severity in both groups were improved only at the end of the treatment period. In left-sided forms, apart for the physician's evaluation [which was not significantly improved in the BDP group and

Table 4. Effects of treatment with BDP or 5-ASA on DAI single parameters in patients with extensive or left-sided ulcerative colitis

	Extensive ulcerative colitis			Left-sided ulcerative colitis		
	Baseline	2 weeks	4 weeks	Baseline	2 weeks	4 weeks
BDP 5 mg/day						
Stool frequency	2.03 (0.11)	1.23 (0.11)[a]	0.65 (0.12)[a]	1.71 (0.10)	1.11 (0.10)[a]	0.59 (0.10)[a]
Rectal bleeding	1.53 (0.12)	1.03 (0.13)[b]	0.31 (0.12)[a]	1.40 (0.09)	0.87 (0.09)[a]	0.37 (0.09)[a]
Physician's rating of disease activity	0.81 (0.10)	0.63 (0.11)	0.23 (0.10)[c]	0.53 (0.08)	0.38 (0.08)	0.17 (0.06)
Mucosal appearance	2.13 (0.11)	—	0.96 (0.17)[a]	2.19 (0.09)	—	1.09 (0.14)[a]
5-ASA 2.4 g/day						
Stool frequency	1.61 (0.20)	0.94 (0.13)[b]	0.83 (0.20)[b]	1.45 (0.09)	0.83 (0.08)[a]	0.42 (0.07)[a]
Rectal bleeding	1.39 (0.18)	0.67 (0.11)[c]	0.50 (0.15)[c]	1.33 (0.07)	0.72 (0.08)[a]	0.32 (0.07)[a]
Physician's rating of disease activity	0.78 (0.13)	0.39 (0.12)	0.33 (0.11)[b]	0.46 (0.07)	0.37 (0.06)	0.16 (0.05)[c]
Mucosal appearance	2.00 (0.14)	—	1.00 (0.20)[c]	1.94 (0.08)	—	0.89 (0.11)[a]

Data expressed as mean (s.e.m.).
[a] $P < 0.0001$ vs. baseline. [b] $P < 0.01$ vs. baseline. [c] $P < 0.001$ vs. baseline.

Table 5. Effects of treatment with BDP or 5-ASA on secondary efficacy variables in patients with extensive or left-sided ulcerative colitis

	Extensive ulcerative colitis			Left-sided ulcerative colitis		
	Baseline	2 weeks	4 weeks	Baseline	2 weeks	4 weeks
BDP 5 mg/day						
Stool consistency	1.75 (0.11)	1.13 (0.11)[b]	0.62 (0.12)[a]	1.57 (0.08)	0.96 (0.11)[a]	0.46 (0.09)[a]
Abdominal pain	1.03 (0.11)	0.47 (0.11)[c]	0.23 (0.08)[a]	1.07 (0.10)	0.53 (0.10)[a]	0.26 (0.08)[a]
Tenesmus	1.19 (0.12)	0.70 (0.14)[b]	0.35 (0.16)[c]	0.93 (0.11)	0.49 (0.09)[a]	0.22 (0.08)[a]
Mucus in stools	1.13 (0.11)	0.67 (0.10)	0.38 (0.11)[c]	1.52 (0.10)	0.87 (0.10)[a]	0.41 (0.09)[a]
5-ASA 2.4 g/day						
Stool consistency	1.72 (0.16)	0.94 (0.13)[c]	0.72 (0.18)[c]	1.38 (0.09)	0.83 (0.09)[a]	0.37 (0.07)[a]
Abdominal pain	1.28 (0.14)	0.50 (0.15)[c]	0.39 (0.16)[c]	0.94 (0.09)	0.42 (0.08)[a]	0.19 (0.05)[a]
Tenesmus	0.72 (0.14)	0.44 (0.15)	0.22 (0.10)[b]	0.91 (0.10)	0.46 (0.08)[a]	0.23 (0.06)[a]
Mucus in stools	0.89 (0.16)	0.56 (0.15)	0.33 (0.14)	1.23 (0.09)	0.63 (0.07)[a]	0.32 (0.07)[a]

Data expressed as a mean (s.e.m.).
[a] $P < 0.0001$ vs. baseline. [b] $P < 0.01$ vs. baseline. [c] $P < 0.001$ vs. baseline.

was improved only at the end of treatment period in the 5-ASA group ($P < 0.001$)], the 2-week and the 4-week improvement ratings of all the other clinical and endoscopic parameters were similar in the two treatment groups.

Safety evaluation

Although they remained within the normal range, mean morning plasma cortisol levels were statistically reduced from baseline in the BDP group: 16.13 ± 0.80 to 11.62 ± 0.79 μg/dL at the end of the treatment period ($P < 0.001$). In 9/67 (13%) of BDP-treated patients cortisol levels fell below 5 μg/dL, but these patients did not show any signs of hypothalamic–pituitary–adrenal axis (HPA) suppression.

At the end of the treatment period, no clinically relevant changes in blood pressure, heart rate, body weight or other haematochemical parameters were observed in both groups. The incidence of adverse events was very low in both treatment groups. Only 2/177 (1.1%) of patients experienced adverse events, which were classified as non-serious: one patient in the BDP group reported menorrhagia and requested discontinuation of the study treatment, and one patient in the 5-ASA group developed influenza symptoms.

DISCUSSION

Corticosteroids and aminosalicylates are the mainstay of treatment for ulcerative colitis flare-ups.[24–26] Since the 1950s, in which the therapeutic efficacy of cortisone in the treatment of active ulcerative colitis was first established,[5, 26] systemic corticosteroids such as prednisolone have become a standard therapy for moderate attacks of ulcerative colitis, but important side-effects, especially those related to interference with adrenal function, have been described.[27] In order to minimise toxicity, rectal formulations have now largely replaced systemic therapies in the management of distal colitis.[28, 29] However, oral therapies are still required when the disease extends more proximally.[24] Furthermore, oral formulations are easier to administer (especially those with the added advantage of once-daily dosing) and are generally more acceptable to the patients. BDP, a corticosteroid with topical characteristics,[30] has proven efficacy and good tolerability when administered as an enema.[9–15] This new oral formulation of BDP has been designed to deliver a powerful anti-inflammatory effect directly to the site of inflammation (by means of its high first-pass metabolism and pH-dependent modified-release system), whilst reducing systemic side-effects such as Cushing-like syndrome and suppression of the HPA axis.

After a preliminary dose-finding study showing that both 5 and 10 mg/day doses have comparable efficacy but that a 5 mg/day dose is generally better tolerated and produces fewer inhibitory effects on plasma cortisol levels,[31] it was found useful to treat active ulcerative colitis with aminosalicylates in conjunction with oral[19] or rectal BDP[32] in order to obtain a prompt mucosal inflammation reduction and improve quality of life.

This controlled study was the first in which the efficacy and safety of oral BDP were assessed in a short-term therapy of mild to moderate active ulcerative colitis in comparison with an established treatment such as delayed-release 5-ASA. The 5-ASA dosage (2.4 g/day, six tablets per day) was chosen because it lies well within the accepted therapeutic range (2–4 g/day)[3, 33] and has a treatment duration (4 weeks) that can be considered sufficient for therapeutic response in patients with this seriousness of active ulcerative colitis.[24] The investigators who performed all the clinical, endoscopic and histological evaluations were blinded to treatment allocation, thus ensuring unbiased assessments, whereas the fact that the patients were not blinded to their assigned therapies must be acknowledged as a limitation of this study. In the absence of a universally accepted efficacy parameter in ulcerative colitis trials, we used the widely employed DAI by Sutherland *et al.*[18] as the main outcome assessment. The two treatment groups were well balanced for demographic parameters and disease duration; however, despite randomisation, the BDP arm included patients with more severe symptoms of active ulcerative colitis than the compared arm.

Both drugs demonstrated anti-inflammatory effects on the colon and rectum, which translated into significant post-treatment clinical, endoscopic and histological improvement, with similar percentages of patients in clinical remission in the BDP group (63.0%) compared with the 5-ASA group (62.5%). Significant differences in the DAI scores from baseline were also observed in both treatment groups even considering extensive or left-sided ulcerative colitis, with patients suffering from extensive forms of ulcerative colitis (transverse colon and pancolitis) treated with oral BDP showing to have a higher probability of achieving a significant clinical and endoscopic improvement after 4 weeks than patients

with the same classification of disease treated with oral 5-ASA ($P < 0.05$ between groups). Histological findings confirmed the clinical results, with a significant decrease in Truelove and Richard's score being achieved in both groups at the end of the treatment period. Considering the more severe symptoms of patients included in the BDP group, the results of oral BDP administration obtained in this study can be considered encouraging. The tendency towards a superiority of once-daily BDP treatment compared with the t.d.s. administration of oral 5-ASA could be confirmed by a higher dosage of BDP. The BDP dose used in this study (5 mg) could have been too low to reach the left or distal colon in sufficient concentrations, or the release of the active ingredient might have been too slow. In fact, the passage of faeces through the distal colon is a fairly rapid process in the active phase of ulcerative colitis,[34] and so the most inflamed parts of the colon might only have been exposed to the drug intermittently and only before defecation. These considerations could explain the better results in patients with extensive disease and the non-significant difference with the comparative arm obtained in patients with left-sided ulcerative colitis.

Therefore, studies of the colonic absorption of oral controlled-release BDP in ulcerative colitis patients are now in progress to clarify how much of an administered dose of BDP is actually delivered and absorbed in different parts of the colon, and if a price in terms of increased adrenal function suppression and side-effects could be paid with a higher dosage of 10 mg/day.

As expected, both treatments were well tolerated (14% patient drop-out), with only one patient in each group reporting adverse events (menorrhagia in a BDP-treated patient and influenza symptoms in a 5-ASA recipient); these were not serious and resolved spontaneously. Despite a statistically significant reduction from baseline values, no patients developed symptoms attributable to HPA axis suppression.

In conclusion, the oral controlled release formulation of topically active corticosteroid BDP, at a dose of 5 mg/day, gave an overall disease improvement in patients with extensive or left-sided, mild to moderately severe active ulcerative colitis, without clinical signs of systemic side-effects derived from HPA axis suppression. Owing to the good safety profile shown by oral BDP in the 4-week treatment of active ulcerative colitis, other studies are in progress to investigate further the dose–efficacy ratio and the interference with HPA function when long-term treatment is suggested.

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