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ORIGINAL ARTICLE

Oral Beclomethasone Dipropionate as an Alternative to Systemic Steroids in Mild to Moderate Ulcerative Colitis Not Responding to Aminosalicylates

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Abstract
Backgroud Aminosalicylates (5-ASA) are first-line treatment for mild-moderate ulcerative colitis (UC). Systemic corticosteroids (CS) are considered for patients in whom 5-ASA has been unsuccessful, but their use is limited by adverse effects. Beclomethasone dipropionate (BDP), a topically acting steroid with low systemic bioavailability, has a more favorable safety profile, but its role in clinical practice is not yet well established.
Aim The aim of the present study is to assess whether oral BDP can be an alternative treatment to systemic CS for patients with mild-moderate UC not responding to first-line therapy with 5-ASA.
Methods From 2003 to 2006, all consecutive patients with mild-moderate UC unresponsive to oral and topical 5-ASA (±topical CS) administered for at least 3 weeks received an 8-week course of oral BDP (10 mg/day for 4 weeks and 5 mg/day for an additional 4 weeks). Co-primary end-points were: (1) clinical remission within 8 weeks, without need of systemic CS; (2) steroid-free remission for 12 months.
Results Sixty-four patients were included. In this study, within 8 weeks, 48/64 patients (75%) entered remission without systemic CS, while 16/64 (25%) failed to enter remission. Within 12 months, 37/64 patients (58%) had prolonged steroid-free remission, while 11/64 (17%) relapsed. During 1 year, 75% of patients receiving oral BDP could avoid systemic CS.
Conclusions Oral BDP can avoid the use of systemic CS in the vast majority of patients with mild-moderate UC not responding to 5-ASA and could be considered as a second-line treatment for these patients.

Keywords Ulcerative colitis · Corticosteroids · Beclomethasone dipropionate · Aminosalicylates

Introduction

Aminosalicylates (5-ASA) are first-line treatment for mild to moderately active ulcerative colitis (UC) [1–3]. Depending on disease extension, oral, rectal or combined therapy is effective for inducing clinical improvement or remission in the vast majority of patients [4–11]. Patients who fail to respond to 5-ASA are usually treated with systemic corticosteroids (CS) as a second-line treatment. Major guidelines recommend a CS course, such as prednisone 40 mg/day, for patients not responding to 5-ASA at an adequate dose (grade of recommendation B or C) [1–3]. There is no clear definition of refractoriness to 5-ASA, but some authors suggest that patients who show no improvement within 2 weeks of high-dose 5-ASA should receive oral CS [12]. Although systemic CS are highly effective for inducing short-term remission, steroid resistance and dependence are relevant problems [13, 14]; in addition, use of systemic CS is limited by a relatively high risk of potentially severe adverse effects [15].

Beclomethasone dipropionate (BDP) is a topically acting corticosteroid characterized by prompt and potent anti-inflammatory activity and low systemic bioavailability which is mainly achieved through first-pass liver metabolism

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[16]. Compared with systemic CS, BDP therefore has the potential advantage of reducing the occurrence of adverse effects by minimizing suppression of the hypothalamic–pituitary–adrenal axis. Rectal administration of BDP, in the management of active distal UC, has been extensively studied and there is consistent evidence of efficacy [17–21]. Conversely, insufficient data is available concerning the role of oral BDP in extensive or left-sided UC. The oral formulation of BDP is constituted by a gastro-resistant methacrylate film coating (Eudragit L100/55) and a modified release core of hydroxypropyl methylcellulose (Methocel K4M) that dissolves at pH values below 6.0. In this way, the drug is firstly released in the distal small bowel and than during passage through the colon [22]. Two randomized controlled studies have shown that an oral dose of 5 mg/day of BDP may be as effective as a standard dose of 2.4 g/day of 5-ASA to induce remission in mild to moderate UC within 4 weeks [23], and that combination treatment (oral BDP plus oral 5-ASA) may be more effective than 5-ASA alone [24]. However, these two studies do not provide clear indications concerning a specific role of oral BDP in clinical management of UC. Furthermore, oral prednisone might not be the most appropriate approach for patients who, even though unresponsive to 5-ASA, do not have severe disease. An alternative, and potentially less toxic, treatment may therefore be preferable.

The aim of the present study was to assess whether a course of oral BDP could represent a useful alternative to systemic CS, as a second-line treatment, in patients with mild to moderately active UC who fail to respond to oral and topical 5-ASA.

Materials and Methods

From January 2003 to December 2006, all patients with mild to moderately active left-sided or extensive colitis, unresponsive to first-line treatment with 5-ASA, were enrolled in the study. Patients were considered unresponsive to 5-ASA if they failed to achieve clinical remission within 3 weeks of treatment with oral mesalamine $\geq$2.4 g/day plus topical mesalamine 2–4 g/day ($\pm$rectal CS). Disease activity was defined according to the colitis activity index (CAI) [25]. CAI is a composite index that includes seven clinical variables [bowel movements, rectal bleeding, global assessment, abdominal pain, fever, extra-intestinal manifestations, and erythrocyte sedimentation rate (ESR)]. CAI score $\leq$4 points indicates clinical remission; a score between 5 and 8 points indicates mild disease, between 9 and 12 points moderate disease, while CAI score >12 points indicates severe disease. Mild to moderately active UC was defined by CAI score between 5 and 12 points.

All patients not responding to 5-ASA received an 8-week course of oral BDP at a standard dose of 10 mg/day for 4 weeks and 5 mg/day for an additional 4 weeks. Oral and rectal 5-ASA was maintained at a stable dose for the 8-week period. At 8 weeks, patients who achieved remission received oral mesalamine 2.4 g/day as maintenance treatment and were evaluated at 3-month intervals for 12 months. Clinical evaluation included CAI score calculation and laboratory tests: ESR, C-reactive protein (CRP), and full blood count. Patients who failed to enter remission or worsened within 8 weeks received systemic CS; patients who showed improvement (defined as 50% reduction in the CAI score), without entering complete remission, received a second course of oral BDP.

Two end-points have been considered: (1) the percentage of patients achieving clinical remission within 8 weeks of oral BDP treatment without need of systemic CS; (2) the percentage of patients maintaining steroid-free remission for 12 months after BDP weaning.

Statistical Analysis

Univariate analysis was performed to compare variables between responders and nonresponders within 8 weeks of BDP treatment and within 12 months after BDP weaning. Categorical and continuous variables were analyzed using the chi-square test and Mann–Whitney test, respectively. Odds ratio (OR) was given with 95% confidence intervals (95% CI) and two-sided *P*-values. A *P*-value <0.05 was considered statistically significant. Multivariate analysis was performed using a logistic regression model to identify clinical variables which predict the response to BDP treatment within 8 weeks in all patients, and within 12 months in patients who achieved short-term remission. The variables considered were: age, gender, disease duration, disease extension, disease activity (mild versus moderate disease), previous systemic CS treatment, and basal CRP values. Kaplan–Meier survival curve was used to assess the cumulative probability of a 1-year course without relapse in patients who achieved remission within 8 weeks of BDP treatment. Analyses were performed using Stats Direct Statistical Tools (copyright © 1990–2001) and Epistat (copyright © Epistat Services, 1991).

Results

A total of 64 consecutive patients with mild to moderately active UC, not responding to first-line treatment with 5-ASA, were included in the study. The clinical characteristics of the patients are outlined in Table 1. After an 8-week course of oral BDP, 48 out of 64 patients (75%; 95% CI 62.6–84.9%) achieved clinical remission (CAI $\leq$4)

Table 1 Clinical characteristics of patients

		All patients $n = 64$	Mild UC $n = 45$	Moderate UC $n = 19$
Age (years)	Mean (range)	47.7 (14–76)	47.4 (14–76)	46.8 (22–76)
Gender	M	33 (52%)	25 (55%)	8 (42%)
	F	31 (48%)	20 (45%)	11 (58%)
Disease extension	Left-sided	33 (52%)	22 (49%)	11 (58%)
	Extensive	31 (48%)	23 (51%)	8 (42%)
Disease duration (months)	Mean (range)	104.5 (1–504)	108.5 (1–504)	99.4 (1–237)
Previous systemic CS treatment	Yes	40 (62%)	28 (62%)	12 (63%)
	No	24 (38%)	17 (38%)	7 (37%)
Disease activity	Mild	45 (70%)	–	–
	Moderate	19 (30%)		
Oral 5-ASA dose	2.4–3 g	7 (11%)	7 (16%)	0 (0%)
	≥4 g	57 (89%)	38 (84%)	19 (100%)
Topical treatment	5-ASA alone	13 (20%)	11 (24%)	2 (11%)
	5-ASA + CS	51 (80%)	34 (76%)	17 (89%)
Basal CAI	Mean (range)	7.4 (5–12)	6.4 (5–8)	9.7 (9–11)
Basal CRP (mg/l) (nv < 5 mg/l)	Mean (range)	10 (1–40)	8.7 (1–40)	11.3 (1–28)
Basal ESR (mmHg/h)	Mean (range)	25 (2–60)	19 (2–60)	29 (2–60)
Basal Hb (g/dl)	Mean (range)	13.0 (9.7–15.7)	13.2 (10.5–15.7)	11.9 (9.7–15.3)

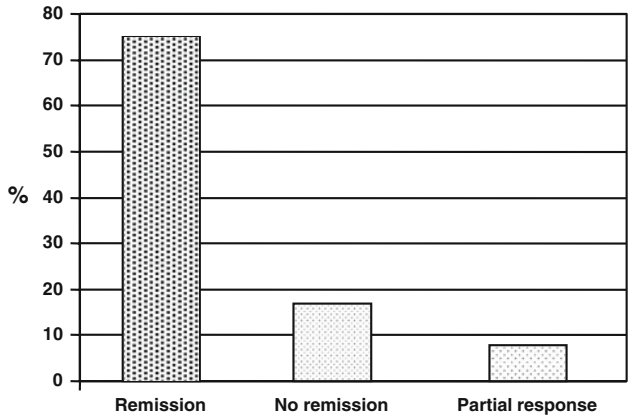

Fig. 1 Short-term outcome after 8-week course of oral BDP in patients with mild to moderate UC not responding to 5-ASA

without systemic CS, while 16 (25%; 95% CI 15.0–37.4%) failed to enter remission. Of these, 11 showed no response or worsened and were switched to systemic CS, while 5 showed partial response and achieved remission after a second course of oral BDP (Fig. 1). Overall, in the entire population, mean CAI score decreased from 7.4 points (95% CI 6.9–7.8) to 3.0 points (95% CI 2.3–3.7) ($P < 0.0001$) after 8 weeks of BDP treatment. Mean CRP values decreased from 9.5 mg/dl (95% CI 7.1–11.9) to 4.8 mg/dl (95% CI 3.2–6.4) ($P < 0.003$).

Patients with moderate disease (CAI 9–12) had a lower remission rate than patients with mild disease (CAI 5–8): 47% versus 87%, respectively ($P = 0.003$; OR = 0.13, 95% CI 0.04–0.43). None of the other clinical variables considered (age, gender, disease duration, disease extension, previous systemic CS treatment, and basal CRP values) were found to be associated with the probability of short-term remission (Table 2). On multivariate analysis, moderately active UC was the only variable independently associated with a reduced probability of remission within 8 weeks (OR = 0.08, 95% CI 0.01–0.38; $P = 0.001$).

One year after BDP weaning, 37 patients (58%; 95% CI 44.8–70.0%) were still in remission, while 11 (17%; 95% CI 8.9–28.6%) had relapsed, of whom 6 received a second BDP course and 5 required systemic CS (Fig. 2). The cumulative probability of a 1-year course without clinical relapse after BDP-induced remission was 94%, 87%, 79%, and 77% at 3, 6, 9, and 12 months, respectively (Fig. 3). None of the clinical variables considered were associated with the risk of relapse in the long term.

Overall, 48 of 64 patients (75%; 95% CI 62.6–84.9%) with mild to moderately active UC not responding to 5-ASA could avoid systemic CS for 1 year. A systemic CS course was required in only 16 out of 64 patients (25%; 95% CI 15.0–37.4%) due to no response to oral BDP in the short term ($n = 11$) or relapse in the following 12 months ($n = 5$) (Fig. 2).

Oral BDP was well tolerated: no serious adverse events were observed. Only 3 out of the 64 patients (4.7%) reported mild CS-related adverse effects (acne in one patient, insomnia in one patient, and mild facies lunaris in one patient).

Table 2 Univariate analysis

		Remission	No remission	OR (95% CI)	*P* value
Age (years)	Mean (range)	47 (14–76)	48 (29–76)	–	0.82
Gender	M/F	24/24	7/9	1.29 (0.41–4.0)	0.77
		50%/50%	44%/56%		
Disease extension	Extensive/left-sided	22/26	9/7	0.66 (0.21–2.05)	0.56
		46%/54%	56%/44%		
Disease duration (months)	Mean (range)	102 (1–333)	116 (7–504)	–	0.67
Previous steroid treatment	Yes/no	28/20	12/4	0.46 (0.13–1.66)	0.37
		58%/42%	75%/25%		
Disease activity	Moderate/mild	9/39	10/6	0.13 (0.04–0.43)	0.003
		47%/87%	53%/13%		
Basal CRP (mg/l)	Mean (range)	10 (1–40)	9 (1–28)	–	0.68

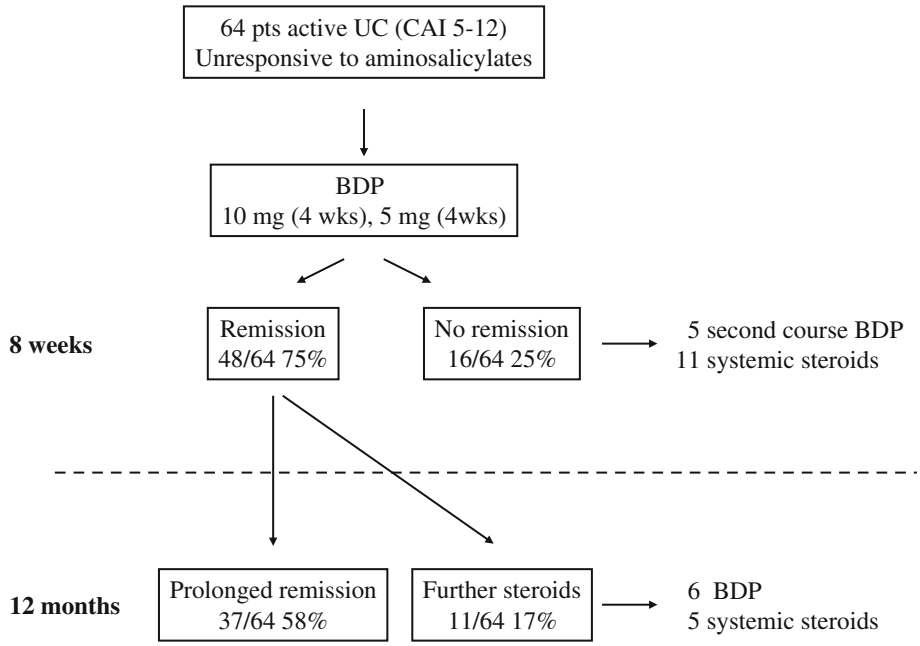

Fig. 2 Course of patients with mild to moderate UC not responding to 5-ASA treated with oral BDP

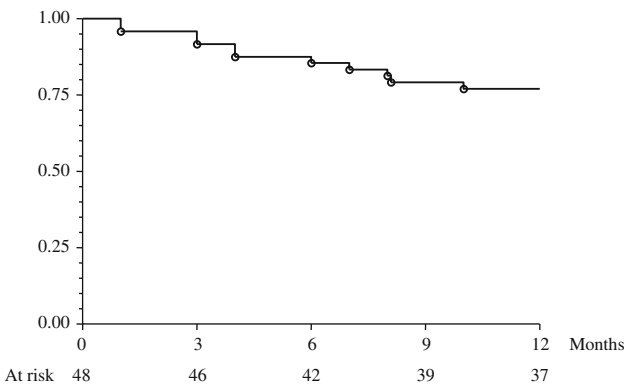

Fig. 3 Cumulative probability of a 12-month course free of relapse in patients with oral BDP-induced remission

Discussion

In the present study, 64 consecutive patients with mild to moderately active left-sided or extensive UC, not responding to 5-ASA, were treated with an 8-week course of oral BDP at a standard dose of 10 mg/day for 4 weeks and 5 mg/day for an additional 4 weeks. The co-primary end-points considered were short-term (within 8 weeks) and long-term clinical remission (12 months) without need of systemic CS.

This study refers to a specific patient population (mild to moderately active UC who failed to respond to 5-ASA) for whom major guidelines recommend second-line treatment with systemic CS [1–3]. However, some controversy still exists regarding the threshold for using systemic CS in mild to moderate UC. Early introduction of oral CS could

be the optimal choice because of their ability to provide prompt relief of symptoms [26], but considering the relevant toxicity of systemic CS, oral prednisone might not be the most appropriate approach for patients who, even though unresponsive to 5-ASA, do not have severe disease. An alternative, and potentially less toxic, treatment may therefore be preferable.

Oral BDP appears to be an interesting option in this setting. The main result emerging from our study is that 75% of our patient population achieved remission within 8 weeks of oral BDP without need of systemic CS and only 17% of patients failed to respond or worsened and required a systemic CS course. Thus if, according to major guidelines, all our patient population was potentially a candidate to receive a systemic CS course, less than 20% effectively received it. Oral BDP appears to be more efficacious in mild disease compared with moderate disease (remission rates within 8 weeks of 87% and 47%, respectively); however, it is worth stressing that approximately 50% of patients with moderate disease entered remission with oral BDP, thus avoiding systemic CS.

One year after BDP weaning, 58% of patients maintained steroid-free remission, while 17% relapsed and required a second BDP course or were switched to systemic CS (Fig. 2). Overall, 75% of patients avoided systemic CS in the short and long term, and this appears to be a relevant aspect considering the good safety profile shown by oral BDP: only 4.7% of patients reported mild and reversible CS-related adverse effects, a figure similar to that reported in previous studies [23, 24].

Considering short- and long-term remission rates, it is interesting to observe that the course of our patient population, with mild to moderate UC treated with oral BDP, is similar to the course of patients with moderate to severe UC treated with systemic CS. In fact, in population-based and referral center studies approximately 80% of UC patients respond to systemic CS in the short term, and approximately 50% maintain remission over 1 year [13, 14]. The high probability of surgery within 1 year after starting systemic CS, as reported in observational studies [13, 14], has not been observed in our patient population with mild to moderate UC: no patient underwent surgery within 1 year after starting oral BDP.

There are some possible criticisms regarding this study: first, the definition of refractoriness to 5-ASA. In the literature, lack of response to 5-ASA is not clearly defined [1–3, 12]. We have arbitrarily considered unresponsive to 5-ASA those patients who failed to enter remission within 3 weeks of at least 2.4 g/day of oral 5-ASA combined with 2–4 g/day topical 5-ASA (±rectal CS). Although, according to some authors, an oral dose of 2.4 g/day of 5-ASA may be suboptimal [27–29], recent studies and systematic reviews suggest that increasing the dose of oral mesalazine formulations does not result in higher remission rates [30–32]. Therefore, simple dose increase of 5-ASA may not be the most effective option for patients who fail to respond to the initial treatment [31]. A dose of topical 5-ASA of 2–4 g/day should be considered optimal according to current evidence: in fact, no dose–response effect has been documented in studies addressing rectal administration of 5-ASA in the management of distal colitis [6, 7]. The second criticism concerns the dose of oral BDP: in this study, oral BDP was administered at a standard dose of 10 mg/day for 4 weeks and 5 mg/day for an additional 4 weeks. This treatment schedule has been arbitrarily chosen: although in a small, open-label, dose-ranging study, it has been shown that 5 and 10 mg/day are equally effective in improving symptoms and endoscopic findings in patients with mild to moderate UC [33], we chose to use the higher dose because our patient population had failed to respond to an appropriate first-line 5-ASA treatment. The third criticism concerns the lack of endoscopic data. The aim of this study was to assess the role of oral BDP in clinical practice for avoiding systemic CS use. In this setting, endoscopy was not routinely performed. Although endoscopy is an important tool in the management of UC and may have relevant prognostic value, it has a relatively low impact on medical treatment in clinical practice. In fact, in the majority of patients, a therapeutic decision can be established on the basis of the clinical picture [34].

In conclusion, a course of oral BDP can be a useful alternative to systemic CS, as second-line treatment, for patients with mild to moderately active UC who fail to respond to appropriate first-line treatment with 5-ASA. The vast majority of these patients, in fact, achieve remission without systemic CS and more than 50% maintain steroid-free remission for 1 year. This issue appears to be relevant to clinical practice.

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