

Oral high dose Beclomethasone dipropionate for treatment of active ulcerative colitis

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Abstract

Oral corticosteroids (CS) have been widely used for treatment of ulcerative colitis (UC) at the price of systemic side effects. Role of topically active oral beclomethasone dipropionate (BDP) in clinical practice is still unclear. The aim of this paper is to investigate efficacy and tolerability of a high dose BDP regimen in mild to moderately active UC. Twenty-five patients (9 males, aged 25-40 years) with mild to moderately active UC, unresponsive to oral and topical 5-ASA (4.8 gr daily) and BDP (5 mg daily), were enrolled. All patients continued 5-ASA plus high dose oral BDP (15 mg od for 4 weeks and then tapered). Clinical, endoscopic, histological and laboratory parameters were monitored. Mean disease activity index (DAI) score at study entry was 8.82±4. Response to treatment was observed in all patients after 2 weeks. Remission was observed in all patients within 4-6 weeks from entering the study (mean DAI score: 2.34±0.5) and maintained throughout 6-month follow-up. No major adverse events were documented. Quality of life global evaluation score improved. This study provides the first evidence of efficacy and safety of high dose oral BDP-scheme in UC demonstrating excellent tolerability and favourable acceptability profile. This new BDP-scheme might be a valid alternative to conventional oral CS when standard dose BDP is not effective. Future studies are needed to explore further clinical indications.

Introduction

Ulcerative colitis (UC), an idiopathic chronic inflammatory bowel disease, is characterized by a spectrum of gastrointestinal (GI) and extraintestinal symptoms related to severity and extent of disease. Treatment of UC may require a long-term complex combination of drugs. Choice of treatment depends on several factors, including age, co-morbidities, severity and extent of disease, and risk of treatment side effects as well as impact on quality of life.¹ In general, rectal formulations are used to control mild to moderate disease limited to the left side. For severe proctitis, distal, left sided disease and for extensive colitis, oral or intravenous preparations are necessary. The most commonly used therapies include 5-ASA and/or corticosteroids (CS) as rectal and oral preparations. Non-responders or steroids-dependant patients need to be upgraded to immunosuppression.² In selected cases, other therapies might be required, such as TNF antagonists or cyclosporine.^{3,4}

Traditionally, conventional CS have been the mainstay for medical treatment of active UC due to their anti-inflammatory properties and interference with the immune response. However, conventional CS are responsible for major systemic side effects due to adrenocortical suppression with consequent negative impact on quality of life.⁵ Main adverse events include Cushing's syndrome, acne, hirsutism, osteoporosis, hypertension, diabetes, psychosis, aseptic necrosis of bone, neuropathy and myopathy. In addition, a proportion of patients depends upon steroids to maintain remission or require several courses of oral or i.v. steroids to control frequent flares-up and are therefore exposed to long-term adverse effects.⁶

In recent years, alternative steroids with a more favourable safety profile have been developed. Beclomethasone dipropionate (BDP) is a topically active steroid with reduced systemic effects due to its extensive first-passage hepatic metabolism. Currently, it is available as rectal suspension enema and oral formulation.⁷ As topical treatment, BDP has been proved to be as effective as conventional CS rectal preparations without interference with the hypothalamic-pituitary-adrenal axis.⁸ For active mild or moderate extensive or left-sided UC, BDP oral preparation (5 mg tablets) is administered at the recommended dosage of 1 tablet od either in combination with 5-ASA or alone.⁹

Since the tablet dissolves at pH values of less than 6.0, the oral delayed-release preparation of BDP is effective in the distal small bowel and throughout the colon.^{10,11}

Despite its promising characteristics and encouraging results, role of BDP in clinical

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practice still needs to be established.

We hypothesized that, in patients with UC matching the criteria for treatment with oral BDP at standard dose (5 mg od) but not responders to therapy, increasing the dose up to 15 mg od (3 tablets) instead of switching to a course of oral conventional CS, would have been an effective and well tolerated alternative with achievement of clinical remission and positive impact on quality of life.

The aim of this study was to investigate efficacy, tolerability and safety of a novel oral high dose regimen of topically acting BDP (15 mg/day) in left-sided or extensive mild or moderate active UC unresponsive to oral 5-ASA and standard dose BDP (5 mg/day).

Materials and Methods

Patients

All patients presenting from March 2006 to January 2008 at the Department of Gastroenterology of the San Raffaele-Giglio Hospital, with left-sided or extensive active UC, Disease Activity Index (Mayo score, or DAI) of ≥3 and ≤10, and a history of previous response (at least one course) to oral conventional CS (deltacortene 1 mg/Kg/day), were treated with oral BDP 5 mg (1 tablet) od and 5-ASA 4.8 gr daily.¹⁰⁻¹³ Patients who clinically failed to respond to treatment after 2 weeks were considered eligible for this single center prospective study.

Table 1 summarises inclusion criteria.

Exclusion criteria were severe renal or hepatic failure, diabetes mellitus, cancer,

osteoporosis, history of drug or substance abuse, active gastroduodenal ulcer, moderate or severe hypertension, pregnancy and breastfeeding. Concomitant treatments during the study period were not allowed except for long-standing therapies for concomitant diseases unrelated to UC and stable dose 5-ASA (4.8 gr daily). Ethical approval was received from the local hospital ethics committee and all patients provided written informed consent prior to entering the study.

Clinical, Endoscopic and Histological evaluation

On initial evaluation, patients underwent medical history collection, complete clinical assessment (vital signs, systolic and diastolic blood pressure, body weight and physical examination) and UC clinical parameters assessment (daily stool frequency, stool consistency, abdominal discomfort, tenesmus, evacuating urgency, rectal bleeding, mucus in the stools, temperature and subjective sense of well-being). All patients underwent a colonoscopy at presentation. Mucosal biopsy specimens were collected from ileum, each segment of the colon (caecum, ascending, transverse, descending and sigmoid) and rectum. At week 8 a flexisigmoidoscopy was performed to evaluate endoscopic score. Laboratory evaluation at enrolment included erythrocyte count, white blood cell count, platelet count, plasma glucose, creatinine, alanine aminotransferase, aspartate aminotransferase, sodium, potassium, magnesium, erythrocyte sedimentation rate (ESR), C reactive protein (CRP). Based on UC clinical parameters and endoscopic mucosal appearance a DAI score was given to each patient, before the first-line treatment (oral BDP 5 mg daily + 5-ASA 4.8 gr daily) and prior to entering the second-line study therapy scheme (BDP 15 mg daily + 5-ASA: 4.8 gr day). Figure 1 describes sequence of events and timing of endoscopic, histological, clinical, haematological and safety profile assessments.

Therapy scheme

Patients who failed to respond to standard dose BDP (5 mg od) treatment were enrolled and received the study treatment. This consisted of 3 tablets of BDP (15 mg) early in the morning for 4 weeks. The dose was then tapered as follows: 2 tablets of oral BDP (10 mg) for 2 weeks followed by 1 tablet of BDP (5 mg) for 12 weeks. Patients also received 5-ASA 4.8 gr daily at a stable dose throughout the study period. Last follow-up was after 32 weeks from entering the study.

Efficacy

Primary outcome measured for efficacy was response to study treatment at week 1.

Secondary outcomes were achievement of clinical remission at week 4 and 6 and maintenance of remission at 6 months from enrolment. Response to treatment was defined as a reduction in DAI score of at least 3 points. Remission was defined as a DAI score < 3 and ESR and CRP within the normal range.

Safety, tolerability and quality of life

Side effects were monitored throughout the study by a questionnaire, completed at the initial visit, after 2 weeks treatment with 5 mg of BDP, and after the end of each course of different dose of BDP. Adverse events such as dyspepsia, insomnia, acne and hirsutism, were evaluated by a binomial score. Effect on pituitary-adrenal function was assessed by clinical evaluation (oedema, Cushing-like syndrome and vital signs such as heart rate, systolic and diastolic blood pressure, and body weight at each visit).

Patients were also asked to compare acceptability of previous courses of oral conventional CS therapy with study treatment scheme.

Impact on quality of life was assessed by a global evaluation on patients' ability to complete normal activities.¹⁴

Results

Forty-eight consecutive patients with left-sided or extensive mild to moderate active UC (17 males, aged 25-65 years) were initially treated with standard dose BDP (5 mg od) and 5-ASA (4.8 gr daily). Twenty-five subjects (aged 25-40 years, 7 males), who failed to respond to initial therapy were enrolled into the study therapy scheme and were administered oral dose BDP (15 mg od) and continued stable dose 5-ASA.

All patients completed the study. Patients' characteristics are summarized in Table 2.

Table 1. Main inclusion criteria.

Inclusion criteria
Mild to moderately active left-sided or extensive UC (Disease Activity Index, DAI score ≥ 3 and ≤ 10)
Clinically unresponsive to 2-week oral BDP 5 mg od and 5-ASA 800 mg tid
Medical history of previous episodes of exacerbation of symptoms treated with high doses of oral conventional steroids plus or not 5-ASA

UC, ulcerative colitis; DAI, disease activity index; BDP, beclomethasone dipropionate.

Table 2. Patients characteristics at study entry (week 2).

Variables	
Age (years)	34 (25-40)
Sex	7 males, 18 females
Body mass index	24 \pm 6
Duration of disease (years)	5.6 \pm 3.8
Extension of disease	17 left-sided, 8 pancolitis
Severity of disease	11 mild, 14 moderate
Previous exacerbation episodes treated with oral high dosage conventional corticosteroids (number)	3.9 \pm 2
Disease activity index score at study entry	8.82 \pm 4

	TIME	Dose	CLINICAL	LABORATORY	ENDOSCOPY	HISTOLOGY	SIDE EFFECTS
S	0	5 mg	X	X	X	X	X
	2 nd wk	15 mg	X				X
T	6 th wk	15 mg	X	X			X
	8 th wk	10 mg	X		X	X	X
D	5 th mo	5 mg	X				X
	8 th mo		X				

Figure 1. Study design: activity of disease and side effects evaluation. BDP, beclomethasone dipropionate.

Efficacy

All patients responded to treatment after 2 weeks from entering the study. Of them, 16 patients (64%) achieved remission within 4 weeks of starting the study treatment, while 9 (36%) within 6 weeks. Clinical remission was maintained in 23 patients at 6 months follow-up (2 patients were lost at follow-up). Endoscopic evaluation performed at entry showed mild to moderate left-sided or extensive UC as summarised in Table 2. Not surprisingly due to the short endoscopic follow-up (8 weeks), mucosal healing was not achieved at repeated flexisigmoidoscopy but only erythema was observed in all patients confirming clinical improvement. At enrolment, mean DAI score was 8.82 ± 4 , while at week 8 (6 weeks after starting high dose oral BDP), mean DAI score was 2.34 ± 0.5 . ESR and CRP mean values were 40 ± 10 and 30 ± 20 at entry, respectively and normalized 4 weeks after starting study treatment in all patients.

Safety and tolerability

The study therapy scheme was generally well tolerated without any serious adverse events. One 20-year old female suffered from acne resolving when BDP was tapered down to standard dose (5 mg od). No significant changes in vital signs such as blood pressure and heart rate or body weight were observed. No clinical features of adrenal suppression were identified. Interestingly, when compared to previous courses of oral conventional CS, treatment scheme appeared generally more acceptable (18 patients recorded score +2) (Table 3). Moreover, 18/25 patients spontaneously reported that the study therapy was very simple, particularly the drug tapering scheme. There were no significant changes in safety laboratory tests, except for the reduction in of ESR and CRP values, which correlated with clinical improvement.

Quality of life evaluation

Impact on quality of life (QOL) was self assessed by the patients. During therapy with high dose BDP an improvement in QOL global evaluation score was observed. Nine patients recorded score 1 at the 6th week while score 0 was reported by all patients at the 8th week (Table 4).

Discussion

The present study provides the first evidence of efficacy, safety and tolerability of a novel, oral, high dose, administration of BDP in patients with left-sided or extensive mild to moderately active UC who had previously required high dose conventional CS for dis-

ease exacerbations and had failed a 2 weeks course of oral standard dose BDP (5 mg). At enrolment, patients had experienced a mean of 3 or more prior flares of the disease, treated with conventional high dose oral CS. Patients responded to study treatment within 2 weeks. Remission was achieved within 4-6 weeks from entering the study (DAI score <3). Treatment was generally well tolerated and no serious adverse events were reported. BDP scheme appeared effective and with an excellent safety profile suggesting that it might be considered a valid alternative to oral conventional CS.

Interestingly, when compared with previous courses of conventional CS therapies, oral high dose BDP scheme scored as more acceptable and very easy in terms of number of pills and drug tapering. QOL evaluation significantly improved in all patients, after 4 weeks of treatment. Particularly, in chronic condition such as UC, QOL is a crucial factor driving treatment choice.¹⁴

The main characteristic of BDP is the first-passage hepatic metabolism allowing achievement of a local potent anti-inflammatory effect inside the bowel with limited systemic activity. This feature suggests a promising key role if used by oral route in UC. In previous studies, the role of rectal formulation of BDP in treatment of UC has been evaluated in comparison with 5-ASA or prednisolone sodium phosphate enemas showing similar efficacy for mild or moderate distal disease.⁸⁻¹⁸ A standard dose of BDP 5 mg od (1 tablet day) has been established in the study conducted by Rizzello *et al.*⁹ In this study, administration of 5 mg or 10 mg daily showed therapeutic equivalence in patients affected by mild to moderate extensive or left-sided UC, whilst morning plasma

cortisol level decreased in the 10 mg group without changes in vital signs. Oral BDP at a standard dose has been studied in treatment of active extensive or left-sided UC, either in combination with 5-ASA or alone resulting effective and safe, without signs of pituitary-adrenal function impairment.¹⁵⁻¹⁸ However, role and dose of BDP in clinical practice is still unclear. Recently, BDP 10 mg od has been safely administered in patients after failure of treatment with 5-ASA achieving clinical remission avoiding use of conventional oral CS.¹⁹ In our prospective study, patients were administered high dose (15 mg) BDP after clinical failure of a 2-week course of standard dose BDP therapy. Therapy scheme was developed on the basis of use of budesonide, another steroid with potent local anti-inflammatory effects specifically in the terminal ileum and limited systemic bioavailability, for Crohn's disease.²⁰ Interestingly, characteristics of responders to standard BDP therapy did not differ from non responders. There was a trend to a lower initial DAI score in responders, not statistically significant due to the small sample size. Moreover, drug tapering, followed by BDP at standard dose (5 mg) for 3 months did not result in clinical signs of interference with HPA axis suggesting that prolonged use might be well tolerated. Despite these encouraging results, this study has multiple limitations, most importantly: small study population due to the strict inclusion criteria and single center setting, absence of a control group and lack of comparison with different BDP doses (*i.e.* initial dose of oral 10 mg of BDP). However, the main limit of the study is that plasma cortisol levels were not measured. Nevertheless, clinical signs of adrenal suppression were not recorded and safety bloods test were very reas-

Table 3. Comparison of previous courses of high dose conventional corticosteroids treatment with beclomethasone dipropionate study therapy scheme.

Score	Tolerance
-2	Previous treatment much more acceptable than current therapy
-1	Previous treatment slightly more acceptable than current therapy
0	Similar acceptability
+1	Current therapy slightly more acceptable than previous treatment
+2	Current therapy much more acceptable than previous treatment

Table 4. Impact of ulcerative colitis symptoms on quality of life.

Score	Impact on quality of life
0	Symptoms not present
1	Mild symptoms
2	Moderate symptoms
3	Severe symptoms that interfere with normal activities
4	Incapacitating symptoms that do not allow patients to continue normal activities

suring. All these factors need to be addressed in further studies to establish the correct dose and duration of oral BDP treatment, and especially to select the target population that might benefit most. Nevertheless, this new regimen might be of value in patients who failed a course of standard dose BDP, as an alternative to conventional steroids in order to avoid systemic adverse events, in steroids-dependant patients or as a bridge to alternative treatment (*i.e.* immunosuppressants).²¹⁻²³

In conclusion, our study shows that high dose oral BDP treatment may prove to be a safe and valid alternative to conventional oral CS in left-sided or extensive mild or moderate UC when BDP 5 mg is not effective with an optimal impact on QOL. Moreover, it suggests that BDP might be useful in other clinical scenarios, such as bridge to immunosuppression or in steroid-dependant patients.

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