Oral Beclomethasone: A Review of its Use in Inflammatory Bowel Disease

Silvio Danese*, Erika Angelucci, Stefano Marconi§, Alessandro Repici and Alberto Malesci

Division of Gastroenterology, Istituto Clinico Humanitas, and §Chiesi Farmaceutici, Parma, Italy

Abstract: Corticosteroids have represented the mainstay of medical treatment for induction of remission in inflammatory bowel disease. Aim of this paper is to review mechanisms of action, safety and efficacy of beclomethasone dipropionate, a steroid with enhanced topical intestinal activity and low systemic activity, in the treatment of inflammatory bowel disease.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel disease (IBD) with a chronic relapsing course. For a number of decades corticosteroids have represented the mainstay of medical treatment of inflammatory bowel disease for the induction of remission.

Corticosteroids have been used for the treatment of IBD since the 1950s because of their potent anti-inflammatory activity and interference with immunological responses. The introduction of corticosteroids in the therapeutic armamentarium has dramatically changed the prognosis and quality of life of IBD patients, avoiding and/or delaying surgery in a great proportion of patients themselves. Several randomized controlled trials (RCTs) have demonstrated the efficacy of systemic corticosteroids in inducing remission in both active UC [1-3] and CD [4,5]. American Gastroenterology Association (AGA) and British guidelines [6,7] as far as European Crohn's and Colitis Organization (ECCO) Consensus [8,9] recommend the use of systemic corticosteroids as first-line therapy for moderately-severely active CD and UC.

However, the therapeutic benefits of systemically available corticosteroids have been limited by the very high incidence of adverse effects, including those related to interference with adrenal function (which varies according to dose and duration of therapy) and Cushing-like syndrome, in addition to acne, infection, ecchymoses, hypertension, diabetes mellitus, osteoporosis, cataracts and glaucoma [10,11]. Furthermore corticosteroids have failed to demonstrate efficacy as a maintenance treatment [12], not only for the above mentioned adverse events but above all for the development of steroid-dependency and/or resistancy, which occur in a high percentage of patients. Population-based studies and open studies reported steroid-dependency and resistancy in more than one third of the patients with IBD who received corticosteroids [13-16].

In the last two decades, efforts have focused on identifying agents with the same ability as corticosteroids to induce remission but with a lower incidence of systemic side effects and the abilty to maintain remission whatever achieved. This has resulted on the one hand in the development of fast-acting biological agents, the use of which is limited by very high costs and unknown long-term safety, and on the other hand in the development of new topically active formulations of corticosteroids, such as beclomethasone dipropionate (BDP) and budesonide [17]. Due to its high affinity for the glucocorticoid receptor and low bioavailability, BDP has emerged as one of the most promising of these new corticosteroids. A recent meta-analysis confirmed that rectal BDP has equal effect as 5-ASA to control symptoms in mild-to-moderate distal active UC [18].

This article provides an overview of the key pharmacological properties of oral BDP and summarises its efficacy and tolerability in clinical trials of patients with IBD. In particular, this review focuses on the published RCTs in the available literature.

PHARMACOLOGICAL PROPERTIES

BDP is a glucocorticosteroid that shows rapid and potent topical anti-inflammatory activity. Its chemical name is 9α-cloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4diene-3,2 dione-17-21-dipropionate [19]. Topical BDP shows high affinity for glucocorticosteroid receptors and limited systemic activity due to extensive first-pass metabolism following absorption from the gastrointestinal tract [20-22]. The metabolite is removed by urinary and biliary excretion.

The major advantage of this limited systemic activity with topical administration is minimisation of systemic effects, such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis and Cushing-like syndrome, which can be seen with traditional corticosteroids [23].

The oral formulation of BDP is constituted by a gastro-resistant film coating that prevents the tablets from dissolving in the stomach, with a modified-release core that ensures drug is released in the distal small bowel and throughout the passage of the colon [24].

Following intravenous dosing, the disposition of BDP and its active metabolite, B-17-MP are characterised by high plasma clearance (150 L per hour and 120 L per hour, respectively), with a small volume of distribution at steady state for BDP (20 L) and larger tissue distribution for B-17-MP (424 L). The terminal elimination half-lives are 0.5 hour and 2.7 hours for BDP and B-17-MP, respectively. Plasma protein binding is moderately high. The renal excretion of

*Address correspondence to this author at the Division of Gastroenterology, Istituto Clinico Humanitas-IRCCS in Gastroenterology, Viale Manzoni, Rozzano, Milan, Italy; Tel: 011-39-3392318230;
E-mail: sdanese@hotmail.com

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BDP and its metabolites is negligible. Faecal excretion is the major route of BDP elimination mainly as polar metabolites [24]. The maximum plasma concentration of B-17-MP obtained after two weeks treatment with BDP 5 mg, once daily per os, appeared to be similar, ie. approximately 1 ng per ml, to the C_{max} observed with a 1 mg dose of BDP administered by inhalation. The systemic availability of B-17-MP evaluated in comparison with an intravenous dose was about 20 % [24].

In four clinical studies and a pharmacological study, suppression of the endogenous cortisol level at the end of 4 weeks' treatment with oral BDP was seen in a percentage up to 25% of patients with UC. However, clinical symptoms associated with adrenal suppression have not been reported [24]. Furthermore, the effect on HPA axis is considered transient and recovery of HPA function is expected after withdrawal of the drug [24].

EFFICACY OF ORAL BDP FOR THE TREATMENT OF UC

The efficacy of oral BDP in UC was initially evaluated in a dose-finding study [25] and subsequently in two randomised, multicentre studies (Table **1**) [26,27].

All studies involved outpatients aged ≥18 years with extensive or left-sided active UC [25-27]. Exclusion criteria included patients with severe UC, or UC in remission. Patients who had been treated with corticosteroids, 5-ASA or sulfasalazine in the month prior to study entry were also excluded [25-27].

In the first randomized double-blind dose-finding trial 25 patients with mildly-to-moderately severe active UC with lesion in the left colon or extensive colitis were enrolled [25]. These patients were randomized to receive an oral gastroresistant controlled-release preparation of BDP 5 mg/day or BDP 10 mg/day or 5-aminosalicylic acid (5-ASA) at inactive dose (1.6 g/day) for 4 weeks (Table **1**). A greater proportion of patients responded to treatment with oral BDP compared with the control group, but this did not reach statistical significance. However, oral BDP significantly improved some individual signs and symptoms of UC, including stool frequency, tenesmus and rectal bleeding (all $p<0.05$ *vs* baseline) [25]. Histological score results reflected changes in the Disease Activity Index [DAI] score and were significantly decreased compared with both baseline and 5-ASA in patients treated with oral BDP. Complete remission was achieved in 16.4%, 43.7% and 21.4% of patients receiving oral BDP 5mg, 10mg and 5-ASA, respectively [25].

Subsequently, in a multicentre RCT 177 patients with mild-to-moderately active UC were randomised to receive BDP 5 mg once time/day (n=90) or 5-ASA 0.8 g t.d.s. (n=87) for 4 weeks [26]. BDP 5 mg/day was compared with 5-ASA in a randomised study and showed that the oral controlled-release formulation of BDP improved DAI score in patients with UC with similar efficacy to 5-ASA ($p< 0.0001$ *vs*. baseline in both groups of treatment) (Table **1**) [26]. Clinical remission was achieved in 63% and 62.5% of patients in the BDP group and 5-ASA group, respectively (no statistically significant difference).

However, post hoc analysis of patients with extensive disease treated with oral BDP showed that these patients were more likely to achieve a significant clinical and endoscopic improvement after 4 weeks than patients treated with oral 5-ASA. The mean DAI score in this subgroup of patients was reduced from 6.50 at baseline to 2.15 at 4 weeks in those treated with oral BDP and from 5.78 to 2.67 in those receiving 5-ASA ($p<0.05$ between treatments). No significant difference in mean DAI scores was seen between the two treatments in a subgroup of patients with left-sided ulcerative colitis. Histological assessment confirmed clinical and endoscopic findings with both groups showing significant reductions from baseline in the mean histological score at the end of treatment. Erythrocyte sedimentation rate (ESR) was also significantly reduced from baseline in both groups indicating improved inflammatory status [26].

Considering BDP as an adjunctive therapy to 5-ASA, we report the data from a further RCT, demonstrating that oral BDP as an add-on therapy to oral 5-ASA was superior to oral 5-ASA alone in the treatment of UC (Table **1**) [27]. In this study 119 patients with mildly-to-moderately active extensive or left-sided UC were randomized to receive oral 5-ASA (3.2 g/day) plus BDP (5 mg/day) (n=58) or oral 5-ASA (3.2 g/day) plus placebo (n=61). Mean DAI was significantly

Table 1. Four-Week, Randomised, Multicentre Studies Evaluating the Use of Oral Beclomethasone (BDP) in Patients with Mild to Moderate Active Extensive or Left-Side Ulcerative Colitis (5-ASA = 5-Aminosalicyclic Acid; DAI= Disease Activity Index; DB = Double-Blind; PL = Placebo; SB = Single-Blind; Tid = Three Times a Day; ‡p<0.05 *vs* Baseline and 5-ASA)

Study	Design	Number of Pts	Treatment (n)	Study Duration	Primary Outcome	Clinical Remission
Rizzello et al., 2001, [25]	DB	25	BDP 5 mg/day (n=19) BDP 10 mg/day (n=19) 5-ASA 1.6 g/day (n=19)	4 weeks	Decrease in DAI and histologicscore	16.7 43.7 21.4
Campieri et al., 2003, [26]	SB	177	BDP 5 mg/day (n=90) 5-ASA 0.8g tid (n=87)	4 weeks	Decrease in DAI	63.0 62.5
Rizzello et al., 2002, [27]	DB, PL	119	BDP 5 mg/day + 5-ASA 3.2 g/day (n=58) PL + 5-ASA 3.2 g/day (n=61)	4 weeks	Decrease in DAI and histologicscore	58.6‡ 34.4

decreased from baseline in both treatment groups, but oral BDP given with 5-ASA also significantly reduced mean DAI scores at the end of treatment more than 5-ASA alone (Table **1**). Several individual variables of the DAI were also significantly improved with oral BDP and 5-ASA versus 5-ASA alone, including rectal bleeding and sense of wellbeing [27]. Rates of clinical remission were significantly higher in the oral BDP and 5-ASA group than with 5-ASA alone (Table **1**). A similar proportion of patients responded to treatment (17.2% *vs* 16.4%) or were unchanged (19.0% *vs* 31.1%); however, significantly more patients in the 5-ASA worsened compared with the combination group (5.2% *vs* 18.0%) [26]. Histological assessment showed a significant improvement with both groups at the end of treatment ($p=0.001$ *vs* baseline) [27]. Other measures of inflammatory status, including mean ESR, erythrocyte, haemoglobin and haematocrit, were all significantly improved in the oral BDP and 5-ASA group (all $p \leq 0.05$ *vs* baseline and 5-ASA alone) [27].

EFFICACY FOR ORAL BDP FOR THE TREATMENT OF CD

In a first small, retrospective, open-label study efficacy and safety were investigated in 34 adults with mild-to-moderate CD or CD in remission [28].

Patients treated with oral BDP 5–10 mg/day for 24 weeks showed a significant mean reduction in Crohn's Disease Activity Index (CDAI) score from baseline at the end of treatment ($p=0.005$ *vs* baseline). The best response to treatment was seen in women, non-smokers and women non-smokers, who all showed significant decreases in CDAI from baseline ($p=0.017$, $p=0.035$ and $p=0.005$, respectively) [28]. At 24 weeks, clinical success [i.e. disease remission (CDAI score <150)] or a marked decrease in disease activity (CDAI reduction of ≥70) was seen in 66.7% of 18 patients who had active disease at baseline [28] Oral BDP maintained disease remission at 24 weeks in 93.8% of 16 patients who were in remission at baseline. Follow-up of these patients for a median 30 months showed that remission was maintained in 60% of patients [28].

In a small, randomized trial, 24 patients with mildly-to-moderately active ileo(-colic) CD were randomized to receive BDP 5mg/day (n=12) or BDP 10 mg/day (n=12) [29]. In the group of patients receiving 5mg/day if the clinical response was not achieved, the dose was modified to 10 mg/day. After remission was achieved, BDP was tapered till stop. If flare-up occurred BDP was started again at the same dose. At 1 month after BDP was started, 16/24 patients (66.6%) were in clinical remission (13 in BDP 10 mg/day group and 3 in BDP 5 mg/day group). Only 2/24 patients (8.3%) had no clinical response (with need for systemic steroids). At 1 year of follow up, 8/24 patients (33.3%) maintained clinical remission, 7/24 (29.1%) needed further cycles of therapy with BDP (for flare-up after BDP stop), while 9/24 (37.5%) was considered treatment failure [29].

The efficacy of beclomethasone dipropionate was also compared to budesonide, another steroid with low systemic effect, in a small RCT on 30 newly diagnosed patients with mild-to-moderately active CD, with inflammatory behavior [30]. Patients were randomized to receive 9 mg/day budesonide or 10 mg/day beclomethasone dipropionate for 8 weeks. The percentage of patients achieving response and remission was superior in patients administered budesonide compared with those administered beclomethasone dipropionate (response: 86.7% *vs* 66.7%, respectively; remission: 66.7% *vs* 53.3%, respectively, $p<0.001$) [30] (Table **2**). However this study has the limitation of small number and therefore larger controlled studies are needed in order to confirm these data.

TOLERABILITY

Oral BDP 5 mg/day was generally well tolerated in clinical trials involving patients with UC and CD. The overall incidence of adverse events was low and ranged between 1.1% and 5.6%; none of the events were considered serious [26-28].

Mean morning plasma cortisol levels in two randomised clinical trials involving patients with UC were significantly reduced from baseline following initiation of oral BDP, but remained within the normal range [26,27]. Reduced cortisol levels (<5 μg/dL) were seen in 13% [26] and 7.5% [27] of BDP-treated patients in these studies, but with no signs of HPA axis suppression. No other clinically relevant changes in blood pressure, heart rate, body weight or other haemato-chemical parameters were observed, except for one patient with reduced plasma glucose and one patient with a reduced platelet count [26,27].

In the retrospective study of patients with CD adverse events that were potentially treatment-related included facial erythema and nausea. One patient presented with elevated fasting blood glucose [28]. In the two other studies in CD, side effects occurred in a very limited number of patients, resulting mild and transient, not requiring any treatment [29,30].

CONCLUSIONS

Corticosteroids are the mainstay of treatment for flare ups of UC and CD. The benefits of traditional corticosteroids in CD are often offset by steroid dependence or steroid-related adverse effects such as interference with adrenal function.

Oral BDP has shown generally similar efficacy to traditional corticosteroids, but with better tolerability. Its limited

Table 2. RCT Evaluating the Use of Oral Beclomethasone (BDP) in Patients with Crohn's Disease (CDAI = Crohn's Disease Activity Index)

Study	Number of Pts	Treatment (n)	Study Duration	Primary Outcome	Clinical Remission
Tursi et al., 2006, [30]	30	BDP 10 mg/day (n=15) BUD 9 mg/day (n=15)	8 weeks	Decrease in CDAI and/or CDAI < 150	66.7% vs 53.3%

systemic activity means that BDP minimises adverse effects that may be seen with traditional corticosteroids, such as Cushing-like syndrome and HPA axis suppression.

Clinical symptoms and mucosal appearance seemed to improve in UC patients when oral BDP 5-10 mg/day was administered as an adjunct or as an alternative to oral 5-ASA in RCTs. While for CD CDAI represents an universally accepted activity index to be used in clinical trials for define response and remission, for UC a similar accepted index does not exist. For this reason results from studies on UC patients are often not directly comparable due to the use of a different index to define response and remission.

Despite decreases in serum cortisol levels at the end of treatment with oral BDP, the mean value remained within the normal range, and no clinical signs or adverse reactions related to adrenal depletion were observed. The overall incidence of adverse events was also low, with no serious events.

Two small studies involving patients with CD indicated that oral BDP 5- 10 mg/day was effective in patients with mild-to-moderate disease, with response to treatment similar to that previously reported with traditional corticosteroids (disease remission rates of up to 70% in patients with mild-to-moderate CD localised to the ileum and/or ascending colon). These results remain to be confirmed in larger, controlled studies.

An induction dose of 10 mg in CD and 5 mg in UC seems to offer some advantage with no increase in systemic side effects.

In conclusion, oral BDP seems to offer an effective and well tolerated treatment for patients with mild-to-moderate active UC and has been shown as potential alternative to traditional glucocorticosteroids in CD placebo-controlled trials and not only non-inferiority trials *vs*. 5-ASA will be soon available showing BDP efficacy versus placebo (S.M., personal data on file).

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