Usefulness of oral beclometasone dipropionate in the treatment of active ulcerative colitis in clinical practice: The RECLICU Study

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Abbreviations: BDP, Beclomethasone dipropionate; UC, Ulcerative colitis; pMS, Partial Mayo score.

⁎ This study has been presented at the following conferences: Digestive Disease Week, New Orleans, USA, 2010, European Crohn’s and Colitis Organisation annual congress, Prague, Czech Republic, 2010.

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Beclometasone dipropionate; Steroids; Ulcerative colitis

Abstract

Background: Beclometasone dipropionate (BDP) is a relatively new topically acting oral steroid to treat mild to moderately active ulcerative colitis (UC). We estimate that 20,000 patients have received oral BDP in Spain in the last two years. Our aim was to evaluate the efficacy and safety of oral BDP in clinical practice.

Methods: Retrospective and multicenter study that included 434 patients with active UC treated with BDP. The partial Mayo Clinic score (pMS, 0–9) was used to measure disease activity. Remission was defined as post-treatment pMS of 0 or 1; response as a decrease in pMS of 3 points or 2 points and ≥30%, and failure as lack of remission or response.

Results: BDP dose was 5 mg/day in 88% of patients and mean treatment duration was 6.2 weeks. BDP achieved remission in 44.4%, response in 22.3% and failed in 33.2% of patients. Mean pMS decreased from 4.9±1.3 to 2.4±2.3 (p<0.0001). Remission rate was higher in mild and moderate than in severe UC (p<0.043) and tended to be higher in left-sided and extensive UC than in proctitis (p<0.06). Failure was less frequent in patients treated for >4 weeks (p<0.02). Mild adverse events were reported in 7.6% of patients.

Conclusion: BDP induces response or remission in two thirds of active UC patients, with a good safety profile. Patients with mild to moderate, left-sided or extensive UC, receiving BDP for more than 4 weeks are most likely to benefit from this treatment.

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1. Introduction

Ulcerative colitis (UC) is a chronic and relapsing inflammatory disorder of the gut that demands long-lasting treatment targeting both flare-up periods and maintenance of remission. Oral systemic steroids have been used to induce remission in patients with active UC for over 50 years due to their potent anti-inflammatory effects. The efficacy of systemic steroids in this setting has been largely demonstrated, becoming the first choice therapy to treat moderate to severely active UC patients. However, the wide range of adverse events associated to these drugs has prompted the search of equally effective but less toxic steroid compounds. The so-called topically acting oral steroids are a group of drugs characterized by a low systemic bioavailability due to an important first-pass liver metabolism aimed at minimizing the amount of drug that reaches the systemic circulation. One of these compounds is oral budesonide which has become the first-line therapy to induce remission in mild to moderate ileo-cecal Crohn’s disease patients. Beclometasone dipropionate (BDP) is another example of topically acting steroid. It was first introduced into the UC armamentarium as a rectal suspension enema for the treatment of distal UC with good efficacy when compared to 5-
oral BDP was associated to a significant clinical, endoscopic and histological benefit after 4 weeks of treatment. In addition, the 5 mg dose was better tolerated and induced a lower reduction of plasma cortisol levels, being equivalent to the 10 mg dose in terms of clinical efficacy.17

Subsequently, Campieri et al. compared oral BDP 5 mg and 5-ASA 2.4 g in a 4-week multicentre, randomized, single-blind study. Both groups of treatment achieved similar global remission rates but remission was more frequently obtained with BDP than 5-ASA in the subgroup of extensive UC patients.18 Rizzello et al. also published a 4-week, double-blind, placebo controlled study in which patients with left-sided or extensive UC were randomized to receive oral 5-ASA (3.2 g/d) along with BDP (5 mg/d) or placebo. The combination of oral BDP with 5-ASA was significantly more effective than 5-ASA alone with no inhibition of pituitary-adrenal function.19 Recently, Papi et al. studied the role of BDP in patients with mild to moderately active UC not responding to 5-ASA. A 4-week course of oral 10 mg/day BDP was followed by a 4-week administration of 5 mg/day in 64 UC patients in which 5-ASA had previously failed. The authors found a remission rate of 75% with most patients achieving 1-year maintenance of remission with no need of further steroid treatment.20 Finally, Balzano et al. evaluated the efficacy of oral BDP and oral prednisone in a mild to moderately active UC population, in an 8-week, multicentre, randomised, double-blind study. Both drugs achieved comparable clinical and endoscopic efficacy, with oral BDP presenting less steroid-related adverse effects.21

Based on the mentioned body of evidence, BDP (5 mg/day) was recently released for marketing in Spain to treat mild to moderately active UC. In the last 2 years, approximately 20,000 UC patients have been treated with BDP in our country. Our purpose was to study the efficacy and safety of oral BDP in the treatment of active UC patients, in clinical practice.

2. Materials and methods

2.1. Study design and definitions

This is a retrospective, multicentre study that included 434 patients with active UC treated with BDP (Clipperr; Chiesi Farmaceutici SpA, Parma, Italy), recruited at 34 Spanish hospitals. Since endoscopy had not been performed before and after BDP treatment in most patients, the partial Mayo Clinic score (pMS, 0–9), including number of bowel movements (0–3), presence of blood in stools (0–3) and physician global assessment (0–3) was used to measure disease activity.22,23 20 patients in whom pre- and/or post-treatment pMS could not be calculated were excluded. Other 20 patients with pre-treatment pMS < 3 were also excluded due to lack of clinically relevant activity, leaving a total of 394 evaluable patients. Disease activity was defined as mild (pMS < 5), moderate (pMS 5 to 7) and severe (pMS > 7). Remission was defined as post-treatment pMS of 0 or 1 and response as a decrease in pMS of 3 points or 2 points with a pMS reduction greater than 30%. Failure was assumed in patients not achieving remission or response. UC disease extension was defined as E1, E2 and E3, according to the Montreal Classification.24 Data regarding demographics, disease description, flare-up severity, dose and duration of BDP treatment, other previous, concomitant or rescue therapy and clinical outcome was collected from patient’s charts.

2.2. Ethical issues and study support

The RECLICU Study was approved by the Ethics Committee of Hospital Clinic i Provincial de Barcelona, Spain. Data was anonymously analysed to preserve patient's confidentiality. This study has been exclusively planned and undertaken by the RECLICU Study Investigators Working Group, which has been fully supported by GETECCU. Chiesi España (the company that commercialises oral BDP in Spain) was not involved in the study design, data analysis or results interpretation.

2.3. Statistical analysis

Qualitative variables were expressed using frequencies. Continuous variables were expressed using mean ± standard deviation. Fisher and Chi-square tests were used to compare qualitative variables. The Student’s t-test was used to compare quantitative variables. All tests were two-tailed with a significance level set at <0.05. Analyses were performed using Stata 10 (Stata Corp., College Station, TX). The Statistical analysis was carried out by the investigators of Hospital Clinic, Barcelona (TN, EA and MS).

3. Results

3.1. Patient characteristics and BDP treatment

Patient characteristics are summarized in Table 1. There were 394 evaluable patients, 197 men and 197 women. Most patients presented left-sided or extensive colitis and almost all patients were on some type of maintenance therapy when BDP was started, being oral or rectal 5-ASA compounds the most frequently used (Table 1). BDP dose was 5 mg/day in 88% and 10 mg/day in 10% of patients (Fig. 1A). The subgroups of patients treated with 5 mg/day and 10 mg/day differed on disease severity and length of treatment but not on other characteristics. A higher proportion of moderate or severe UC was found in the 10 mg/day group (75%) than in the 5 mg/day group (53%, p < 0.007) and patients receiving BDP 10 mg/day were treated for a longer period of time (9.7 ± 6.7 weeks) than patients receiving BDP 5 mg/day (6.2 ± 3 weeks; p < 0.003). Global mean BDP treatment duration was 6.2 ± 3.8 weeks. Only few patients received BDP for less than 4 weeks, being their treatment duration 1 or 2 weeks in most of the cases. Approximately half of patients was treated for 4 weeks, which is the regime recommended in the drug label,
and the rest of patients received BDP for more than 4 weeks (5–18 weeks) (Fig. 1B). Apart from the already mentioned difference on BDP dose, the subgroups of 4 weeks and more than 4 weeks of treatment did not differ on any other characteristic. At the time of starting BDP, other treatment modifications were done in a significant proportion of patients, being the addition of oral or topic 5-ASA or an increase in the dose of oral 5-ASA the most commonly found (Fig. 2).

3.2. Efficacy of BDP

BDP was associated with remission in 175 patients (44.4%), response in 88 patients (22.3%) and failed in 131 patients (33.2%) (Fig. 3A). Mean pMS decreased from 4.9 ± 1.3 before BDP treatment to 2.4 ± 2.3 after BDP treatment, (p < 0.0001) (Fig. 3B). When considering the efficacy of BDP in different subgroups of UC patients, we found that remission rate was significantly higher in mild and moderate than in severe UC (p < 0.04) (Fig. 4A). In addition, a trend towards a higher remission rate in left-sided and extensive UC than in proctitis was observed (p < 0.06) (Fig. 4B). Patients under immunosuppressive and/or biological maintenance treatment showed a lower remission rate compared to patients under other maintenance treatments or no treatment (p < 0.006) (Fig. 4C). In respect to other changes introduced in patient’s treatment when BDP was started, there was no significant difference in remission rates depending on other added treatment (p < 0.4) (Fig. 4D). Patients under BDP treatment with 5 and 10 mg achieved comparable remission rates (p < 0.9) (Fig. 5A). Finally, patients treated with BDP for more than 4 weeks presented less failure than patients treated during 4 weeks (p < 0.02) (Fig. 5B). As shown in Table 2, this effect was independent of BDP dose.

3.3. Safety of BDP

Mild adverse effects were reported in 7.6% of patients, Table 3. Cushing like symptoms were only present in 7 patients (1.1%), being the most common adverse effect found, followed by cephalae (1.3%), nausea/vomiting (0.76%) and menstrual disturbances (0.76%). Mild infections (oral candidiasis and upper respiratory infection) were reported in only 2 cases (0.5%). In respect to drug safety in different BDP dose groups, we found that 6% of patients (22 individuals) on 5 mg/day and 20% of patients (7 individuals) on 10 mg/day dosage reported an adverse effect. Although the presence of an adverse effect was significantly more frequent in the 10 mg/day group (p < 0.01), it’s difficult to draw any conclusion on dose safety due to the low number of reported adverse events in the series. Finally, there was no difference in safety regarding patients on 4-week-treatment regime compared to patients with more than 4 weeks of BDP therapy.

3.4. Rescue therapy

Systemic steroids were introduced as rescue therapy in most patients failing BDP treatment (31.7%). In addition, cyclosporine (2.3%) or infliximab (3.6%) were also used in a few patients. Only 6.6% of UC patients required hospitalization and 1% underwent colectomy after BDP treatment (Fig. 6).
4. Discussion

This is the first study reporting on the efficacy and safety of oral BDP in the treatment of active UC patients in clinical practice. In this study, more than 40% of patients achieved clinical remission and two thirds of them presented clinical response upon oral BDP treatment. Both figures are slightly smaller than those reported previously. The reasons for these differences are multiple. First, and probably the most important, the criteria used to define remission and response. In our study we used pMS, which is based on number of bowel movements, presence of blood in stools and physician global assessment (0–9), because endoscopy had not been performed before and after BDP treatment in most patients. We defined remission as pMS of 0 or 1 after BDP treatment, a criteria more stringent than that used in most previously published studies, in which remission was defined by a pMS of 0, 1 or 2, in a 0–12 scale. Another reason contributing to the mentioned differences between our work and previous studies is the criteria applied for patient selection. Whereas in our study all UC patients treated with BDP were included in the analysis, to obtain a more complete picture of the efficacy and safety of oral BDP in clinical

![Figure 2](https://academic.oup.com/ecco-jcc/article-abstract/4/6/629/648781 by guest on 26 December 2018)

**Figure 2** Other treatment changes at BDP start. Each bar represents the percentage of patients in which treatment was modified when BDP was started.

![Figure 3](https://academic.oup.com/ecco-jcc/article-abstract/4/6/629/648781 by guest on 26 December 2018)

**Figure 3** BDP efficacy. A) Global efficacy of BDP treatment: each bar represents the percentage of patients achieving remission, response or failure under BDP treatment; B) Mayo score pre/post BDP treatment: box plot graphic displays the distribution of pMS before and after BDP treatment.

![Figure 4](https://academic.oup.com/ecco-jcc/article-abstract/4/6/629/648781 by guest on 26 December 2018)

**Figure 4** Factors influencing BDP-induced remission. Bars represent the percentage of patients that achieved remission under BDP treatment, according to UC severity (A), extension (B), maintenance treatment (C) and changes in treatment (D).
practice, previous studies selected the UC patients according to age (18–70 years), disease extension (left-sided or extensive UC), disease activity (mild to moderate), absence of concomitant serious diseases, and other requirements on concomitant treatment at study inclusion.

In addition to defining the global efficacy of oral BDP in clinical practice, we were also able to evaluate the efficacy of this drug in different subgroups of UC patients. The remission rate was significantly higher in mild and moderate than in severe UC. Few patients with severe UC were treated with BDP in our study, since BDP has been specifically launched to treat mild to moderate UC, as disclosed in the drug label. However, the very low remission rate found in our few severe UC patients clearly support the notion that systemic steroids, and not oral BDP, are the appropriate treatment in this potentially life-threatening situation, as recently recommended in the ECCO guidelines.3 The fact that patients under immunosuppressive or biological maintenance treatment had a lower remission rate than patients receiving mesalazine or no maintenance treatment also supports this concept, since the need of immunosuppressive or biologic therapy undoubtedly identifies a subgroup of more severe and more difficult to manage UC patients.

In respect to disease extension, there was a trend towards a higher remission rate in left-sided and extensive colitis than in proctitis. In fact, oral BDP has been designed to reach the proximal colon and, for that reason, all previously published studies evaluating oral BDP considered proctitis an exclusion criteria. As discussed for severe UC, although the number of patients with proctitis included in our study was relatively low, our results clearly demonstrate that patients with proctitis should not be treated with oral BDP.

Conversely to a previously published clinical trial,19 we were unable to demonstrate the superiority of combined oral BDP. In fact, none of the treatment changes introduced at the time of BDP start significantly influenced remission rates to the BDP therapy. The most likely explanation is the fact that more than 80% of our UC patients already were on oral 5-ASA maintenance treatment when BDP was introduced.

As expected, close to 90% of patients were treated with BDP 5 mg/day, the recommended dose in the drug label, whereas 10% of them received 10 mg/day. We found no differences between both doses in respect to BDP efficacy. Our results are in keeping with the first, BDP dose-finding study, conducted by Rizzello et al., in which both doses were equally effective. In that study the 10 mg/day dose caused a greater inhibition of the pituitary–adrenal axis,17 providing the rational to use the 5 mg/day dose, which was chosen in most subsequently published BDP clinical trials.18,19

### Table 2

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<tr>
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<td>N: 148</td>
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<tr>
<td>Failure: 59 (33.5%)</td>
<td>Failure: 33 (22.2%)</td>
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<tr>
<td>10 mg dose</td>
<td>N: 11</td>
<td>N: 26</td>
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<td>Failure: 6 (55%)</td>
<td>Failure: 6 (23%)</td>
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### Table 3

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<th>Frequency</th>
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<tr>
<td>Cushing like symptoms</td>
<td>7</td>
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<td>Cephalgia</td>
<td>5</td>
<td>1.27%</td>
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<tr>
<td>Nausea/vomiting</td>
<td>3</td>
<td>0.76%</td>
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<td>Menstrual disturbances</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Asthenia</td>
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<tr>
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<td>Skin lesions</td>
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<tr>
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### Figure 5

Efficacy of BDP treatment according to dose and therapy duration. Bars represent the percentage of patients that achieved remission, response or failure according to A) BDP dose and B) treatment duration.

### Figure 6

Rescue therapy after BDP treatment. Each bar represents the percentage of patients receiving different medical rescue therapies or requiring colectomy.
found a higher proportion of moderate and severe disease in patients treated with 10 mg/day, which might have influenced the efficacy in this subgroup of patients. This difference in respect to disease severity in addition to the low number of patients treated with 10 mg/day in the series makes BDP efficacy comparisons between the two BDP dose groups difficult in our study.

One of the most relevant findings of our study was the fact that patients treated for more than 4 weeks failed BDP therapy less frequently than patients treated for 4 weeks. Differences seemed to be truly dependent on duration of BDP treatment, since disease extension and severity were comparable in the two groups and the potential confounding influence of BDP dose was specifically ruled out. Our results therefore suggest that duration of BDP treatment should be longer than 4 weeks, which is the recommended length of BDP treatment in the drug label. The fact that all previously published clinical trials only used 4 weeks of BDP treatment is really surprising if we take into account that other well established treatment options for mild to moderate UC, such as oral 5-ASA and systemic steroids, are used in this setting for a minimum of 8 to 12 weeks. In that regard, a very recently published, non-controlled study, using for the first time a 8-week course of BDP in mild to moderately active UC patients previously not responding to 5-ASA has reported the highest response and remission rates published so far, which might also support the notion that more than 4 weeks of treatment are required to successfully manage mild to moderately active UC with BDP. Although encouraging, these results require to be confirmed due to the uncontrolled nature of the study and the relatively small number of patients included in it.

Systemic steroids were introduced as rescue therapy in most patients failing BDP treatment. We can assume that this treatment had a high efficacy after BDP failure, based on the relatively low proportion of patients that required additional treatment with ciclosporine or infliximab. Considered together, these results suggest that the failure of BDP, which occurs in one third of UC patients, can be successfully managed introducing systemic steroids, leaving the colectomy rate as low as 1%.

Finally, our study also provides interesting data regarding oral BDP safety. Although the retrospective nature of our study is an obvious limitation to address this issue, the fact that no serious adverse events were identified and mild adverse events were only found in 7.6% of the cases in this cohort of 394 UC patients, points towards an excellent safety profile of this drug. Our results are in keeping with those of a double-blind trial, very recently presented at the ECCO 2010 Meeting, in which patients receiving BDP experienced less steroid-related side effects than patients treated with oral prednisone.

In conclusion, our study is the first aimed at defining the usefulness of oral BDP in clinical practice, a scenario in which BDP is more frequently used associated with some type of maintenance therapy. It demonstrates that this drug is efficacious and safe in the treatment of active UC. Oral BDP induces remission in more than 40% and response in two thirds of UC patients. Patients with left-sided or extensive, mild or moderately active UC that are treated for more than 4 weeks present the best outcome in response to oral BDP.

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Statement of authorship:
All authors have made substantial contributions to the conception and design of the study, acquisition, analysis and interpretation of data, in addition to drafting and revising the manuscript.

References