Oral Budesonide Versus Prednisolone in Patients With Active Extensive and Left-Sided Ulcerative Colitis

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See editorial on page 2000.

Background & Aims: **Systemic glucocorticosteroids (GCSs) have proven efficacy in active ulcerative colitis but cause undesired systemic side effects. Therefore, new GCSs with high topical activity and a high rate of metabolism may be of clinical value in this condition. The aim of this study was to explore the efficacy and safety of the topically acting GCS budesonide in an oral controlled-release formulation in extensive or left-sided, mild to moderately active ulcerative colitis.** ***Methods:*** **A 9-week, randomized, double-blind, controlled trial was performed, and treatments with 10 mg budesonide or 40 mg prednisolone daily, both gradually tapered, were compared. Endoscopic improvement and effect on endogenous plasma cortisol were assessed.** ***Results:*** **Thirty-four patients were administered budesonide, and 38 patients were administered prednisolone. Mean endoscopic scores improved significantly in both groups but without difference between the groups. Five patients in the budesonide group and 7 patients in the prednisolone group deteriorated and were withdrawn from the study. Morning plasma cortisol levels were suppressed in the prednisolone group (entry, 449 nmol/L; 2 weeks, 116 nmol/L; 4 weeks, 195 nmol/L) but were unchanged in the budesonide group.** ***Conclusions:*** **The GCS budesonide administered in an oral controlled-release formulation seems to give an overall treatment result in active ulcerative colitis approaching that of prednisolone but without suppression of plasma cortisol levels. This concept merits further evaluation.**

Budesonide is a highly potent glucocorticosteroid (GCS) with a high affinity for the GCS receptor. It is readily absorbed and rapidly degraded to metabolites with low GCS activity during the first passage through the liver[1] and, thus, has a low systemic availability. Budesonide in enema form (2 mg/100 mL) has been evaluated and has been proven to be superior to placebo[2] and to be as efficacious as conventional prednisolone[3–5] or mesalamine retention enemas.[6] No, or only limited, suppression of endogenous plasma cortisol has been noted.[2–5] An oral formulation of budesonide optimized to release the drug in the ileum and ascending colon has been developed for the treatment of Crohn's disease. This formulation has been shown to be superior to placebo[7] and comparable with oral prednisolone[8] but causes significantly fewer GCS-associated side effects.

In severe to moderately severe attacks of UC, conventional GCSs have been proven to be the most efficacious medical treatment to induce remission and to alleviate symptoms.[9] In moderately severe attacks of UC, a course of oral prednisolone or prednisone is usually the therapy of choice, with or without concomitant mesalamine or sulfasalazine treatment.

The aim of this explorative pilot study was to evaluate the efficacy of an oral formulation of budesonide, optimized to release the drug throughout the colon, vs. a standard regimen of oral prednisolone in the treatment of active extensive and left-sided UC. Furthermore, the safety and tolerability of budesonide was evaluated, including the impact on endogenous plasma cortisol production.

Patients and Methods

Patients

Both hospitalized patients and outpatients, aged at least 18 years, were eligible for inclusion. All patients gave their informed signed consent before entry. Criteria for inclusion were a definite diagnosis of mild to moderately severe active UC extending proximally beyond the sigmoid colon as verified by colonoscopy at entry. Endoscopic activity had to

Abbreviation used in this paper: GCS, glucocorticosteroid.

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be a score of at least 2 (see below) in one or more colorectal segments, and disease symptoms had to include blood in stools and at least three bowel movements per day before entry (excluding days before colonoscopy).

Exclusion criteria included diabetes, untreated hypertension, and clinically significant liver disease. Patients being treated with H_2-receptor antagonists or proton pump inhibitors and patients who had been administered GCSs other than oral contraceptives during the 2 weeks preceding the trial were also excluded. A history of GCS hypersensitivity, pregnancy, and breast-feeding were also exclusion criteria.

Concomitant therapy for UC was not allowed, with the exception of oral sulfasalazine, mesalamine formulations, or olsalazine. If any of these drugs were used, the dose had to be kept constant during the last 2 weeks before and throughout the trial. Other drugs necessary for the patient's well-being were administered at the discretion of the investigator.

Investigational Drugs

Budesonide capsules and the corresponding placebo were manufactured by Astra Draco AB (Lund, Sweden). The capsules contained acid-resistant pellets with a sustained-release profile to deliver the active drug during the passage throughout the colon. The reference drugs, prednisolone tablets (2.5, 5.0, and 10 mg) and placebo tablets, were manufactured by Hydro Pharma A.S. (Elverum, Norway). The drugs were delivered in blister packages, and the patients were administered one dose in the morning (containing budesonide capsules and placebo prednisolone tablets or vice versa) and one dose in the evening (containing either a budesonide capsule or a placebo budesonide capsule). During the last 2 weeks of the study, only a morning dose was administered.

Study Design and Treatment Plan

The study was of randomized, double-blind, double-dummy design with two parallel groups, and the total treatment time was 9 weeks. The patients were randomly allocated to treatment with either oral budesonide or oral prednisolone from blocks of four at each of the participating nine centers.

Budesonide was administered in a dose of 6 mg in the morning and 4 mg in the evening during the first 4 weeks and was tapered to 4 mg in the morning and 4 mg in the evening during treatment weeks 5–7 and to 4 mg in the morning during weeks 8–9. Prednisolone was administered as a single morning dose throughout the study, starting with 40 mg daily during the first 2 weeks and then was tapered by 5 mg per week until week 8, when 7.5 mg was administered as one daily dose with a final dose of 5 mg daily during week 9. The patients were followed up as outpatients with visits to the clinics after 2, 4, and 9 weeks. Patients were withdrawn from the study if their clinical status seriously deteriorated or if no improvement at all was observed after 2 weeks. Other reasons for treatment discontinuation were serious complications, adverse events, or pregnancy.

The patients were asked to return all unused medication at

Table 1. Scoring of Endoscopic Inflammation at Colonoscopy and Flexible or Rigid Sigmoidoscopy

Score	Endoscopic findings
0	Normal/noninflamed mucosa
1	Granularity, edema, and lack of normal vascular pattern
2	Hyperemia, friability, and petechiae (and all of score 1)
3	Ulcerations (and all of score 1 and 2)

NOTE. The scores were subdivided as moderate or intense by the investigator.

ing unopened blisters at the local hospital pharmacy. Patients were considered compliant if they had taken at least 75% of the medication.

Assessments

Clinical symptoms. Diary cards were used for registration of daily bowel movements (i.e., number of movements, quality of stools, and presence of blood and/or mucus). Data from the days before colonoscopy were not used in the analysis.

Endoscopy. Disease extent and severity of mucosal inflammation were assessed by the use of flexible colonoscopy at entry and after 4 weeks of treatment. A flexible or rigid sigmoidoscopy was performed after 2 and 9 weeks of treatment. The macroscopic appearance of the mucosa was classified using a four-grade scoring system[2,3,5] (Table 1) in each of five predetermined colorectal segments at colonoscopy (ascending colon, transverse colon, descending colon, sigmoid colon, and rectum) or in the sigmoid colon and/or the rectum at sigmoidoscopy.

Histopathology. Mucosal biopsy specimens were obtained from each segment of the colon and rectum and always from the most severely affected area in each segment. Biopsy specimens were fixed in formalin, embedded in paraffin, stained with H&E, and evaluated in a blinded manner by an independent histopathologist (R.W.). The degree of inflammation in the histological specimens was then graded according to Florén et al.[10] In this scale, a score of 1 represents essentially normal mucosa, and a score of 5 represents the most severe inflammatory changes.

Clinical chemistry and hematology. Blood samples for assessment of hematology (erythrocyte sedimentation rate, hemoglobin, erythrocyte count, and leukocyte count with differentials and platelets) were taken at entry and after 2, 4, and 9 weeks. Assessment also included determination of blood glucose, serum orosomucoid, albumin, and creatinine levels, as well as liver function tests. Morning blood samples (taken between 7 and 9:30 AM) were drawn at each visit for analysis of plasma cortisol. These samples were frozen and later analyzed at one central laboratory (Astra Draco AB) using a high-performance liquid chromatography method.[11]

Statistical and Ethical Considerations

The primary study variables were the changes in endo-

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Table 2. Demography and Disease History in Patients Treated With Either Oral Budesonide or Prednisolone for Active UC

	Budesonide	Prednisolone
No. of patients	34	38
Sex (M/F)	21/13	21/17
Age[a] (*yr*; range)	33 (18–67)	34 (19–71)
Duration of UC[a] (*yr*; range)	0.8 (0–39)	2.2 (0–23)
Current attack[a] (*day*; range)	34 (0–100+)	43 (1–100+)
Involvement		
Extensive colitis	21	22
Left-sided colitis	13	16
Maintenance treatment with mesalamine drugs (%; median dose [*g*])	20 (59; 2.0)	18 (47; 2.0)

[a]Values are expressed as the median.

different colorectal segments for each patient were reduced to one by taking the maximum. The histopathologic scores were analyzed in the same way.

Endoscopic remission was defined as a score of 0, and histopathologic remission was defined as a score of 1. Responders were defined as those patients whose scores were reduced compared with those at entry. Remission and response rates were analyzed after 4 weeks. Clinical symptoms, as recorded in the patients' diaries, were reduced to averages over 2-week periods. Changes in laboratory parameters and in clinical symptoms were secondary variables.

The study was designed to have 80% probability of detecting a difference of about 0.8 in the change of endoscopic score with Wilcoxon rank sum test at the 5% level. This goal was not based on clinical relevance but seemed realistic compared with previous studies with GCS enema preparations in UC.[2–5] Furthermore, in those studies, the use of the endoscopic scoring system showed that endoscopic improvement correlated well with both clinical and histological improvement, as well as with remission rates. The calculation was based on 20 evaluable patients per group. It was decided that a group size of 35 patients would be used to compensate for early withdrawals.

The primary analysis was based on the all-patients-treated and the last-value-extended principles. For endoscopic and histopathologic scores, two-way analysis of variance was applied to the changes from entry with the factors treatment, time, and treatment by time. χ^2 tests (with Yates' correction) were used for the analysis of remission and response rates and for the proportion of plasma cortisol values of <150 nmol/L. Student's t test was used for all other variables. P values of ≤ 0.05 were considered statistically significant.

Because this was a pilot study with mainly an exploratory purpose and no aim of proving differences, no compensation for multiple comparisons was made.

The study was performed in accordance with the principles stated in the Declaration of Helsinki, and approvals from the Swedish Medical Products' Agency and the local Ethics Com-

Results

Patient Enrollment and Treatment Discontinuations

A total of 75 patients were randomized, and 72 patients were actually treated with one of the study drugs. The study groups were well matched with respect to age, sex, length of current attack, disease extent, and maintenance treatment (Table 2). Of the 38 patients receiving mesalamine maintenance therapy, 1 patient was treated with mesalazine (Pentasa; Ferring AB, Malmö, Sweden), 3 patients with olsalazine (Dipentum; Pharmacia AB, Uppsala, Sweden), and 34 patients with sulfasalazine (Salazopyrin; Pharmacia AB).

Thirty-four patients were treated with budesonide, and 38 patients were treated with prednisolone. Sixteen patients, 8 in each group, were withdrawn from the study. The reasons for treatment discontinuations are shown in Table 3. No patient was considered noncompliant.

Efficacy

The mean endoscopic scores are shown in Figure 1. The mean decreased with time significantly in both groups. After 9 weeks, the mean decrease was 1.20 in the budesonide group compared with 1.36 in the prednisolone group ($P = 0.12$; two-way analysis of variance). When the scores were analyzed separately for each of the five colorectal segments, a significantly greater improvement was observed in the sigmoid colon for the prednisolone group after 4 weeks ($P = 0.04$) (Figure 2). The 95% confidence intervals for the differences in the decrease of the endoscopic scores between the budesonide and prednisolone groups were -0.1 to $+0.8$ at 2 weeks, -0.2 to $+0.8$ at 4 weeks, and -0.4 to $+0.7$ at 9 weeks. The corresponding confidence intervals for the changes in histological scores were 0.1–1.2, 0.1–1.3, and 0.0–1.4. Negative values represent better efficacy for budesonide.

Four of 31 patients remaining in the budesonide group after 4 weeks were in endoscopic remission (defined as an endoscopic score of 0 in all colonic segments) com-

Table 3. Reasons for Treatment Discontinuations in 16 Patients

Reason	Budesonide	Prednisolone
Disease deterioration	5	7
Adverse event	2[a]	1[b]
Withdrawal of informed consent	1	0

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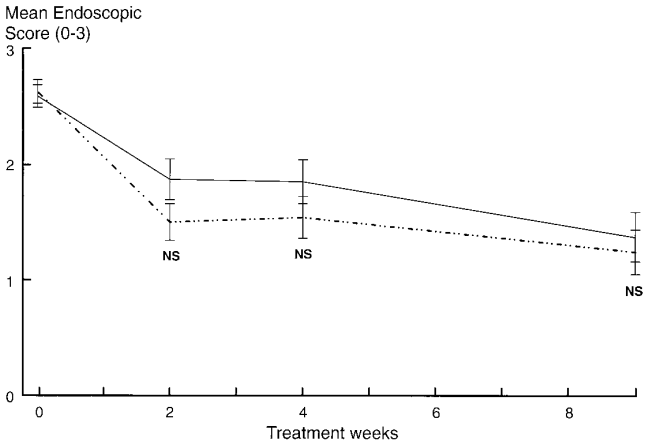

Figure 1. The effect of budesonide capsules (——) and prednisolone tablets (– · · – · · –) on the mean endoscopic scores (from entry to 2, 4, and 9 weeks). All patients treated and last-value-extended principle. Values are expressed as mean ± SEM.

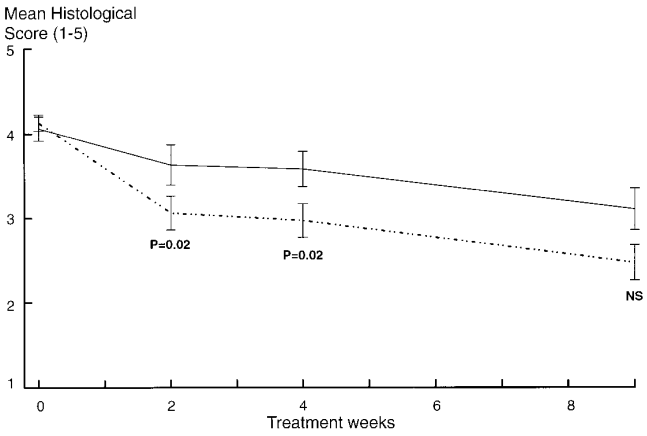

Figure 3. The effect of budesonide capsules (——) and prednisolone tablets (– · · – · · –) on the mean histological scores (from entry to 2, 4, and 9 weeks). All patients treated and last-value-extended principle. Values are expressed as mean ± SEM.

pared with 6 of 36 patients in the prednisolone group ($P = 0.93$). At the same time, 21 patients in the budesonide group were classified as responders compared with 25 patients in the prednisolone group ($P = 1.00$). There were no significant differences in the endoscopic scores between patients with extensive or left-sided colitis. The histopathologic scores were significantly reduced compared with baseline in both treatment groups. The reduction in histopathologic scores was significantly greater in the prednisolone group ($P = 0.022$; two-way analysis of variance) (Figure 3). A separate analysis for each of the colorectal segments showed that the better effect of prednisolone was limited to the descending and sigmoid segments of the colon, where a significant difference was found at 4 weeks (Figure 2). Three of 31 patients were in histological remission in the budesonide group after 4 weeks vs. 6 of 36 patients in the prednisolone group ($P = 0.63$). Eleven patients in the budesonide group had improved histopathologic scores compared with 22 in the prednisolone group ($P = 0.065$).

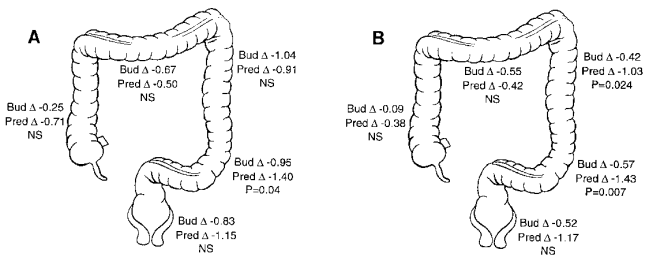

Figure 2. Mean (*A*) colonoscopic and (*B*) histopathologic activity scores in each of the five colorectal segments at entry and after 4 weeks of treatment with either budesonide (Bud) or prednisolone

There was no significant difference between the two treatment groups with respect to change in endoscopic score when stratification was made for smoking habits (nonsmoker, ex-smoker, or current smoker) ($P = 0.15$). On the other hand, endoscopic improvement was significantly greater ($P < 0.01$) for smokers than for nonsmokers and for ex-smokers, regardless of treatment (Table 4). Both treatment groups improved in terms of bowel symptoms during the course of the study. However, there were no significant differences between the two treatment groups at any time point with regard to number of bowel movements and mucus discharges with or without blood.

Safety

No changes in blood pressure were detected in the two groups, but weight gain at the final follow-up was significantly greater in the prednisolone group ($P = 0.042$). There were no differences in blood chemistry and hematology parameters except for a slight but significant ($P = 0.017$) elevation of the leukocyte count in the prednisolone group after 2 weeks. A significant decrease in platelet count and orosomucoid levels was also ob-

Table 4. Effect of Smoking Habits on Endoscopic Score After 4 Weeks of Treatment

	Changes in mean endoscopic scores from entry	
	Budesonide	Prednisolone
Nonsmokers	−0.5 (n = 16)	−0.9 (n = 20)
Ex-smokers	−0.4 (n = 8)	−0.9 (n = 10)
Current smokers[a]	−1.9 (n = 6)	−1.8 (n = 6)

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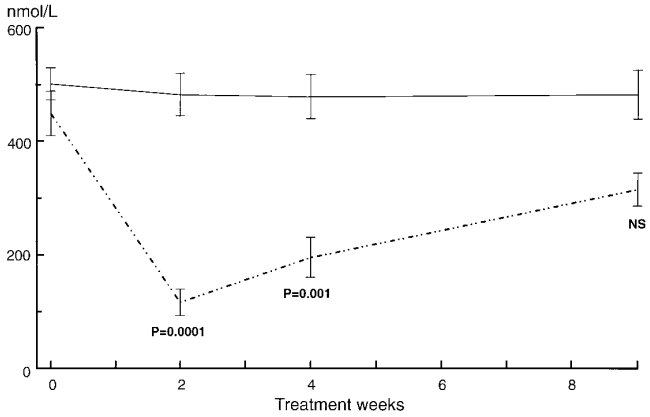

Figure 4. Plasma cortisol levels during treatment with oral budesonide (——) or prednisolone (– · · – · · –) for active UC. All patients treated and last-value-extended principle. Values are expressed as mean ± SEM.

served in the prednisolone group. Other clinical chemistry, including liver function tests, did not show any clinically relevant changes attributed to the treatment.

Mean plasma cortisol levels were unchanged in the budesonide group during the entire study period, whereas the levels in the prednisolone group were significantly depressed after 2 and 4 weeks of treatment (Figure 4). No patient in the budesonide group had a plasma cortisol level less than the lower reference limit of 150 nmol/L at any time during the study vs. 25 of 33 patients in the prednisolone group after 2 weeks ($P < 0.001$), 21 of 34 patients after 4 weeks ($P < 0.001$), and 6 of 34 patients after 9 weeks ($P = 0.047$).

Adverse events were generally mild in both groups and caused discontinuation of the treatment in 3 patients. One patient in the budesonide group discontinued treatment because of vomiting in combination with deterioration of disease, and 1 patient discontinued because of a rash. One patient treated with prednisolone discontinued treatment because of insomnia (Table 3).

Another patient in the budesonide group with primary sclerosing cholangitis had moderately elevated alkaline phosphatase values at entry and had a significant increase during the study. As the colitis symptoms subsided, the levels decreased, and any casual relationship with the study drug was considered unlikely. One patient in the prednisolone group developed a Cushing-like syndrome. One patient in the budesonide group developed pneumonia, but the study drug was continued unaltered, and the patient improved after being treated with antibiotics. One patient in the prednisolone group developed severe edema of the legs requiring hospitalization and treatment with diuretics. In general, the patients in the budesonide group had a higher incidence of gastrointestinal tract treated patients showed a greater tendency for adverse events from the central and peripheral nervous system (3% vs. 13%).

Discussion

This is the first controlled pilot study of UC in which oral budesonide has been compared with prednisolone. The overall endoscopic evaluation did not yield any statistically significant differences between the two regimens, although in the analysis of the effect on endoscopic score in the separate colorectal segments, prednisolone was superior in the sigmoid colon after 4 weeks of treatment. Thus, budesonide seems to have an anti-inflammatory effect in most of the colon and in the rectum approaching the effect of prednisolone. The effect of budesonide seems to be mainly topical, as indicated by the lack of suppression of endogenous plasma cortisol levels.

From the results of other trials,[2–5] it was expected that budesonide capsules would have some, albeit limited, effect on plasma cortisol levels. The fact that budesonide capsules in the doses and the pharmaceutical formulation used in this trial did not affect plasma cortisol levels in this trial may be partly because of the high first-pass metabolism of the drug, but it is more likely because of an incomplete release of budesonide, particularly in the distal colon. The latter is supported by the fact that a 9-mg dose of budesonide in another pharmaceutical formulation with a faster drug-release profile suppressed basal plasma cortisol levels in the order of 40% in patients with active Crohn's disease.[8,12] Further data are awaited from absorption and pharmacokinetic studies.

Early trials of cortisone in the 1950s established the efficacy of corticosteroids in the treatment of active UC.[9] Prednisolone has since become the standard drug for moderate attacks of UC, administered in a dose of approximately 40 mg daily for the first few weeks and then decreased as soon as the disease responds to treatment. This regimen is considered to give optimal response with minimal side effects. However, the dosage is dependent on therapeutic traditions, and intial doses may vary between 30 and 60 mg in different countries. Side effects have been shown to be dose dependent.[13]

In this study, treatment with prednisolone tended to be more efficacious than treatment with budesonide. There may be several reasons for this outcome. One explanation may be that the budesonide dose was too low and did not reach the distal colon in sufficient concentrations or that the release was too slow, considering that the passage of feces through the distal colon is a fairly rapid process in the active phase of UC.[14] After defecation

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