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The use of oral topically acting glucocorticosteroids in the treatment of inflammatory bowel disease

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GLUCOCORTICOSTEROIDS are the mainstay of treatment of active Crohn's disease and ulcerative colitis. These drugs however carry important cosmetic short-term side effects and when used long-term they induce severe irreversible complications. Topically acting glucocorticosteroids, especially budesonide, have been designed to achieve local effect at the site of inflammation without systemic effects of the drug. The first results of clinical trials are promising and budesonide has been shown to have an improved safety with almost comparable efficacy in comparison with prednisolone. The optimal enema dose seems to be 2 mg/100 ml at night whereas 9 mg o.m. is the optimal dose to treat ileal or right ileocolonic Crohn's disease. Topically acting GCS, like standard GCS are not effective for maintenance of remission of Crohn's disease or recurrence prevention after resection of the involved Crohn's segment.

Key words: glucocorticosteroids, Crohn's disease, ulcerative colitis, budesomide, prednisolone, remission

Introduction

A glucocorticosteroid can have a selective topical action when the drug acts at the level of the mucosa and is almost not absorbed. Examples are prednisolone metasulphobenzoate and hydrocortisone foam. Other steroids are readily absorbed but undergo a very rapid first pass metabolism resulting in very low systemic blood levels. Examples are bethamethasone dipropionate, budesonide and fluticasone propionate. Tixocortol pivalate is characterized by low absorption and high first pass. The most suitable glucocorticoids for topical therapy are budesonide and fluticasone propionate.

The efficacy and safety of topical enema therapy using the new glucocorticosteroid budesonide in distal colitis are already well established. Recent developments in the use of this drug for peroral therapy in Crohn's disease is of great interest. Oral formulations are also under study for the treatment of ulcerative colitis. We will focus this review mainly on the use of topically acting glucocorticosteroids in Crohn's disease.

In past years numerous attempts have been made to develop glucocorticosteroids with high topical activity lacking the systemic activity of the drug and hence carrying less side effects.

The ideal topically acting glucocorticosteroid should have sufficient water solubility for a homogeneous distribution in the bowel lumen. A high uptake rate should be combined with sustained binding at the level of the target tissue with deep penetration into the bowel wall. There should be a high affinity for the steroid receptor and high intrinsic activity at this level. Hepatic first pass inactivation should be maximal. Candidate drugs are budesonide, fluticasone propionate and beclomethasone dipropionate.

Budesonide, however, has the best profile since its water solubility is 100 times higher than that of the two latter drugs. Crohn's disease is mostly located in the ileocolonic region of the bowel whereas isolated colonic disease occurs in about 30% of the patients and isolated proximal small bowel disease is very rare. Therefore formulations used should release the drug at the very site of the diseased bowel. Entocort® capsules release budesonide in a controlled manner in the ileum resulting in an absorption of 52–79% in the ileum and the right colon.[1] The drug is largely metabolized on first pass through the liver resulting in a bioavailability of 9–12% Preliminary studies indicate that plasma concentrations in patients with active Crohn's disease might be higher than in normal volunteers.[2] The influence of feeding with this preparation on pharmacokinetics does not seem to be important.

Budenofalk® (oral pH dependent release budesonide) results in absorption of budesonide after 2–4 h, the rate being influenced by feeding in an important manner. Measurements of excretion in ileostoma bags showed that 25–37% of the budesonide of this formulation enters the colon.[3]

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Trials with Budesonide in Ileal and Right Ileocolonic Crohn's Disease

Open trial with entocort®

Löfberg *et al.*[4] studied the efficacy and safety of controlled ileal release budesonide in an open uncontrolled trial. Twenty-one patients with active Crohn's disease involving the distal ileum, the ileocaecal area or the ascending colon entered the trial. The patients received budesonide CIR in a dose of 3 mg t.d.s. for 12 weeks, followed by tapering to 2 mg t.d.s. for 6 weeks and finally to 1 mg t.d.s. for an additional 6 weeks. Primary variables of efficacy were a modified Crohn's disease activity index (mCDAI), laboratory parameters of activity and plasma cortisol levels. The mean mCDAI level at entry amounted to 268 (± 71 SD) and decreased to 146 (± 91) at 4 weeks, 122 (± 87) at 12 weeks ($P < 0.001$). There was also a significant decrease of ESR during the study period. Eighteen patients responded favourably during the first 12-week treatment period and 13 completed the trial. No serious side effects occurred. The mean plasma cortisol levels decreased but remained within normal range. Four patients were markedly suppressed on the highest dose of budesonide.

Controlled trials with entocort®

In a double-blind multicentre Canadian dose finding trial[5] 258 patients were randomly assigned to receive placebo or one of three doses of budesonide–39 or 15 mg daily. The drugs were given in two divided doses in the morning and the evening. The primary outcome measure was clinical remission as defined by a score of 150 or less on the Crohn's activity index. Changes in the quality of life were also assessed with an inflammatory bowel disease questionnaire. Serum corticotropin stimulation tests were also performed. After 8 weeks of treatment, remission occurred in 51% of the patients in the group receiving 9 mg of budesonide (95% confidence interval, 39–63%), 43% of those receiving 15 mg (95% confidence interval, 31–55%) and 33% of those receiving 3 mg (95% confidence interval, 21–44%) compared with 20% of those receiving placebo ($P < 0.001$, $P = 0.009$ and $P = 0.13$ respectively). Improvements in the quality of life paralleled these remission rates. Location of disease, prior surgical resection, and previous use of corticosteroids did not affect the outcome. Budesonide caused a dose-related reduction in basal and corticotropin-stimulated plasma cortisol concentrations but was not associated with clinically important corticosteroid-related symptoms or other toxic effects.

A European multicentre study group conducted a randomized double-blind 10-week trial[6] comparing the efficacy and safety of an oral controlled-release form of budesonide with the efficacy and safety of prednisolone in 176 patients with active ileal or ileocaecal Crohn's disease (88 patients in each treatment group). The dose of budesonide was 9 mg per day for 8 weeks and then 6 mg per day for 2 weeks. The dose of prednisolone was 40 mg per day for 2 weeks, after which it was gradually reduced to 5 mg per day during the last week. Again the primary outcome parameter was the CDAI score with remission defined as a score of 150 or less. Three objective parameters of inflammation were also assessed including ESR, C-reactive protein and orosomucoid.

At 10 weeks, 53% of the patients treated with budesonide were in remission compared with 66% of those treated with prednisolone ($P = 0.12$). The mean score on the Crohn's disease activity index decreased from 275 to 175 in the budesonide group and from 279 to 136 in the prednisolone group ($P = 0.001$). ESR, CRP and orosomucoid decreased more in the prednisolone group than in the budesonide group but the difference was significant only for ESR. Corticosteroid-associated side-effects were significantly less common in the budesonide group (29 vs. 48 patients, $P = 0.003$). Two patients in the prednisolone group had serious complications (one had intestinal perforation and one an abdominal wall fistula). The mean morning plasma cortisol concentration was significantly lower in the prednisolone group than in the budesonide group after 4 weeks ($P < 0.001$) and 8 weeks ($P = 0.02$) of therapy, but not after 10 weeks.

An International Budesonide Study Group[7] investigated the efficacy and safety of two different dosage regimens of budesonide, 9 mg once daily (o.m.) in the morning and 4.5 mg twice daily in comparison with prednisolone 40 mg in one dose daily. In this multicentre trial 177 patients with active Crohn's disease (CDAI > 200) were randomly assigned to one of the three treatments for 12 weeks. The budesonide dose was tapered to 6 mg after 2 weeks and to 3 mg after 10 weeks.

Prednisolone was tapered to 30 mg after 2 weeks and then gradually to 5 mg during the last 3 weeks. Efficacy was measured based on remission rates, with remission being defined as CDAI $\leq$ 150. During therapy disease activity rapidly decreased in all groups. After 2 weeks the remission rate amounted to 48% in the budesonide (o.m.) compared with 37% in the prednisolone group. At 8 weeks similar remission rates were observed in the budesonide (o.m.) and prednisolone groups (both 60%) compared with 42% in the budesonide b.i.d. group. The proportion of patients with corticosteroid-associated side-effects was not significantly different in the three groups but the proportion of patients with moon face was significantly higher in the prednisolone group. At 8 weeks mean morning plasma cortisol levels were significantly less suppressed in both budesonide groups than in the prednisolone group. Impaired

adrenal function as assessed by a short ACTH stimulation test was also significantly more common in the prednisolone group than in the budesonide group.

Budenofalk® versus 6-methylprednisolone

In this study[8] only 67 patients with active Crohn's disease were included. Thirty-four patients were treated with 3 × 3 mg per day of budesonide and 33 with 6-methylprednisolone 48 mg per day with tapering. At eight weeks 55.9% of the budesonide patients achieved remission versus 72.7% in the 6-methylprednisolone group. The difference was not significant. There was a greater decrease, although not significant, of the CDAI in the 6-methylprednisolone group than in the budesonide group (BUD: 263 ± 50 to 118 ± 69; M-Pred: 262 ± 81 to 95 ± 61). Steroid related side effects appeared in 28.6% of the patients in the budesonide group and in 69.7% in the 6-methylprednisolone group (P = 0.0015).

Dose finding study with budenofalk®

A recent dose finding study[9] comparing three doses of Budenofalk, 3 × 2 mg, 3 × 3 mg and 3 × 6 mg in active Crohn's ileocolitis yielded remission rates (CDAI < 150) after six weeks of treatment in 36%, 55% and 66% of the patients respectively. The mean CDAI decreased from 257 ± 77 to 202 ± 103 in the 3 × 2 mg group, from 268 ± 75 to 140 ± 83 in the 3 × 3 mg group and from 239 ± 63 to 116 ± 57 in the 3 × 6 mg group. Mean basal plasma cortisol levels were decreased by 21.7% (3 × 2 mg), 48.7% (3 × 3 mg) and 59.4% (3 × 6 mg). Glucocorticosteroid associated side effects occurred in 20% (3 × 2 mg), 21% (3 × 3 mg) and 31% (3 × 6 mg) of the patients. Unfortunately in this study no control group treated with standard glucocorticosteroids was included. Therefore a comparison of the ratio efficacy to safety is not possible.

Budesonide for Maintenance Therapy of Crohn's Disease

Entocort® and prolongation of remission

During a 1 year follow-up study of the European multicentre trial[6] 90 patients with active Crohn's disease in the terminal ileum of the ileocaecal area who were in remission (CDAI-score ≤ 150) after 10 weeks' treatment with either oral Entocort® or oral prednisolone, were randomized to receive continued treatment with either Entocort® 6 mg or 3 mg daily, or placebo for up to 1 year in order to prevent relapse.[10] A relapse was defined as an increase of the CDAI-score above 150 points, and at least 60 points above the baseline, or deterioration of the disease that required other treatment.

This double-blind, controlled, randomized trial involved 11 centres in six European countries. The 6 mg group had significantly longer median time to relapse or discontinuation of treatment compared with the placebo group (258 vs. 92 days; P = 0.02). An adrenocorticotropic hormone (ACTH)-test performed after 3 months was normal in all 13 patients (100%) remaining in the placebo group at this stage of the study, compared with 19 out of 22 patients (86.4%) in the Entocort® 3 mg group, and 18 out of 23 patients (78.3%) in the Entocort® 6 mg group. There were no statistically significant differences between the three treatment groups. Glucocorticosteroid-related side effects were mild (i.e. moon-face, acne) and mostly related to previous prednisolone treatment.

A continuation of the Canadian multicentre study[5] of Entocort® vs. placebo for active Crohn's disease was designed in a similar way to the European maintenance trial. One hundred and five patients with inactive Crohn's disease in the ileum or ileum and proximal colon received continued treatment with either placebo or oral Entocort® 3 or 6 mg daily in a 12-month, double-blind, randomized trial.[11]

The Entocort® 6 mg group also fared better in this study, with median time to relapse or discontinuation of therapy of 178 days, vs. 124 days in the 3 mg group, and 39 days among placebo-treated patients (P = 0.026). However, the rate of relapse did not differ significantly between the three treatment groups after 12 months of treatment; 61% of the patients in the Entocort® 6 mg treatment group had relapsed after 12 months, compared with 70% in the Entocort® 3 mg treatment group and 67% in the placebo group (P = 0.75). The relapse rates at 1 year were in agreement with the results documented from the European study.

Basal levels of plasma cortisol did not differ between the three study groups during the trial. A dose-dependent reduction in ACTH-stimulated cortisol concentration was found, but was not associated with clinically important steroid-related side effects.

Budenofalk® and maintenance of remission

Budenofalk 3 × 1 mg/day is not more effective to maintain remission of Crohn's disease put into remission with glucocorticosteroids than placebo.[12] The proportion of patients in remission after 3, 6 and 12 months was 66%, 44% and 35% in the budesonide group and 62%, 42% and 29% in the placebo group.

It is not clear why maintenance therapy with standard glucocorticosteroids and also with topically acting glucocorticosteroids including budesonide is not effective. Down-regulation of glucocorticosteroid-receptors might be a reason. Rogler *et al.*[13] recently reported on a decrease of mucosal intracellular glucocorticoid receptors in the colonic mucosa in patients with IBD independent from therapy, whereas no decrease in systemic levels were observed.

In an elegant study V. Gross *et al.*[14] demonstrated that patients chronically treated with standard glucocorticosteroids for Crohn's disease successfully can be switched to oral pH-dependent release budesonide (Budenofalk®) and that the success of the switch was dose dependent, 9 mg of budesonide being the most effective dose. One can argue, however, that in that manner prednisolone dependent patients become budesonide dependent patients which presents only borderline advantages in the long term. This condition might better be managed by starting the patients on immunosuppression.

Postoperative recurrence prophylaxis

In a study comparing budesonide 6 mg/day every morning with placebo, the frequency of endoscopic recurrence did not differ between the groups (intent-to-treat analysis) at 3 months (45% vs. 46%) or at 12 months (63% vs. 63%).[15] The recurrence rates were, however, different with respect to the indication for surgery. There was no difference between treatments in patients who had undergone surgery for fibrostenosis, whereas endoscopic recurrence rates were lower in the budesonide treatment group, both at 3 months (21% vs. 47%; $P = 0.012$) and at 12 months (32% vs. 65%; $P = 0.048$) in patients who had undergone surgery for disease activity.

Budesonide for Induction of Remission in Crohn's Disease: Comparison with 5-ASA

In a pivotal-study Thomsen *et al.*[16] showed that budesonide 9 mg o.m. (Entocort®) is significantly more efficacious than mesalazine 2 g b.i.d. to induce remission in ileal and right ileocolonic Crohn's disease. Remission rates with budesonide were 44%, 48%, 69%, 64%, 62% after 2, 4, 8, 12 and 16 weeks compared with 37%, 39%, 45%, 42% and 36% for mesalazine ($P < 0.01$ at 8, 12 and 16 weeks). Adverse effects were similar in both groups. Twenty per cent of the patients in the budesonide group had decreased adrenal function.

Conclusion

Budesonide is a valuable approach for developing topical therapy of IBD with glucocorticosteroids. Entocort releases the drug more proximally and is very suitable for the treatment of ileal and right ileocolonic disease. Budenofalk releases more budesonide in the colon and might be more suitable to treat colonic disease although data are lacking. Budesonide is as effective as standard glucocorticoids to induce remission in ileal and right ileocolonic Crohn's disease with less side effects. One morning dose of 9 mg is probably the optimal dose although more studies are necessary.

Prolonged treatment with 6 mg of Entocort prolongs remission but does not maintain it over one year. Therefore pulse therapy should be preferred.

The exact place of budesonide in the clinical management of Crohn's disease and ulcerative colitis has still to be defined.

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