INFLAMMATION AND INFLAMMATORY BOWEL DISEASE

Budesonide treatment of collagenous colitis:
a randomised, double blind, placebo controlled trial with
morphometric analysis

O K Bonderup, J B Hansen, L Birket-Smith, V Vestergaard, P S Tejlbyærg, J Fallingborg

Background: Collagenous colitis is characterised by diarrhoea, lymphocytic inflammation, and a thickened subepithelial collagen layer in the colorectal mucosa. No standard treatment of the disease is established.

Aims: To investigate the clinical and histological effect of oral budesonide (Entocort, AstraZeneca) in the treatment of collagenous colitis.

Patients: Twenty patients with collagenous colitis (collagen layer >10 µm) and diarrhoea (>4 stools/day and/or stool weight >200 g/day).

Methods: A randomised, double blind, placebo controlled trial of budesonide treatment. Patients were randomised to placebo or budesonide for eight weeks. Stool frequency and stool weight were registered before and after treatment. Sigmoidoscopy was performed before and after treatment, and biopsies at fixed locations were obtained for morphometric analysis.

Results: Ten patients were randomised to budesonide and 10 to placebo. All 10 patients receiving budesonide had a clinical response compared with two in the placebo group (p<0.001). In the budesonide group, stool weight was reduced from 574 g/day to 200 g/day and stool frequency was reduced from 6.2/day to 1.9/day (p<0.01). The histological inflammation grade in the sigmoid mucosa and the thickness of the collagen layer were significantly reduced. A correlation between the grade of inflammation as well as collagen layer thickness and stool weight was found. No side effects were reported. Eight of 10 patients had relapse of symptoms within eight weeks after stopping treatment.

Conclusions: Budesonide is a highly effective and well tolerated treatment of collagenous colitis. There is a high risk of relapse after stopping eight weeks of treatment.

The first case of collagenous colitis was described in 1976 by Lindström and now the disease is recognised as a distinct clinicopathological entity. It is characterised by chronic watery diarrhoea. Endoscopic examination reveals only minimal or absent mucosal changes. In biopsies from the colon mucosa, a characteristic abnormal thickening of the subepithelial collagen layer as well as lymphocytic infiltration of the epithelium and the lamina propria is found. The aetiology and pathogenesis of collagenous colitis are still unknown but it appears to be caused by mucosal injury from a luminal factor. Some observations indicate that the faecal stream contains the noxious agent but the nature of this luminal factor is unknown. Observations on patients with collagenous colitis after faecal stream diversion could indicate that this pathogenic agent is transmitted from the small bowel.

Large studies of treatment of collagenous colitis have not been performed and no standard treatment has been established. Therapy is based on single case reports and several uncontrolled small series. In a retrospective study, treatment with non-specific antidiarrhoeals, 5-ASA, or prednisolone was recommended.

Budesonide is a topical acting corticosteroid released in the small intestine and the ascending colon. It is characterised by a high receptor binding affinity and a high first pass metabolism in the liver. In controlled clinical trials budesonide was shown to be effective in the treatment of inflammatory bowel disease. In two uncontrolled studies and in one placebo controlled study budesonide also seemed to be of therapeutic benefit in collagenous colitis. The aim of this study was to investigate the clinical and histological effect of budesonide in the treatment of collagenous colitis.
METHODS

Patients
In this study, patients at least 18 years old with clinically active collagenous colitis were included. Diagnostic criteria for collagenous colitis were histological findings of a collagen layer more than 10 µm located beneath the surface epithelium in colonic mucosa. Clinical activity was defined as a daily stool frequency of >4 or stool weight >200 g/day. Patients treated with anti-inflammatory drugs (aminosalicylates, corticosteroids, azathioprine) within the last three months were excluded. Additional exclusion criteria were other chronic gastrointestinal diseases. Stool samples for pathogens, parasites, and ova should be negative. Patients with clinically significant renal or hepatic disease and pregnant or breast feeding women were ineligible. The protocol was approved by the local ethics committee and all participants provided written informed consent. Thirty two patients who attended our outpatient clinic for collagenous colitis were evaluated for the trial. Twenty patients (16 women and four men) fulfilled the study criteria and accepted participation. Median age was 54 years (40–80).

Methods
The study was a randomised, double blind, placebo controlled trial. Patients fulfilling the study criteria were randomised to receive placebo or active treatment with budesonide for eight weeks (9 mg for four weeks, 6 mg for two weeks, and 3 mg for two weeks). The budesonide formulation used was a gelatin capsule containing acid stable micro granules (Entocort 3 mg; AstraZeneca). The capsule dissolves at a pH of 5.5 or higher. This formulation releases budesonide in the distal part of the ileum and ascending colon. The placebo medication was identical in appearance. No anti-inflammatory medication other than the study drugs was allowed. Concomitant antidiarhoeal drugs were allowed except during periods of stool weight determination.

At entry, patient demographic data and medical history were recorded. In all patients routine laboratory analyses and stool cultures were performed. Before and after treatment current clinical symptoms were recorded. Stool frequency and stool weight were assessed for three days. Sigmoidoscopy was performed before and after treatment with biopsies at fixed intervals in the distal 40 cm of the colon. The primary efficacy end point was clinical remission defined as a reduction in stool frequency or stool weight of >50%. After stopping treatment patients were followed for eight weeks for signs of relapse of clinical symptoms.

Histology
Biopsy specimens from all patients were reviewed independently by two experienced pathologists (VV, PST). Two biopsy

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<thead>
<tr>
<th>Table 1 Baseline characteristics of patients</th>
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<tr>
<td>Placebo (n=10)</td>
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<td>Budesonide (n=10)</td>
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<td></td>
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<tr>
<td>Sex (male/female)</td>
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<td>0/10</td>
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<td>4/6</td>
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<td>Age (y)</td>
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<tr>
<td>57 (40–80)</td>
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<tr>
<td>51.5 (42–71)</td>
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<td>Duration of symptoms (y)</td>
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<td>8.5 (1–23)</td>
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<td>7 (1–25)</td>
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<tr>
<td>Stools/day (n)</td>
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<tr>
<td>4.5 (2.3–10)</td>
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<tr>
<td>6.2 (2.7–7.3)</td>
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<tr>
<td>Stool weight/day (g)</td>
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<tr>
<td>463 (229–1280)</td>
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<tr>
<td>574 (241–853)</td>
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<td>Sigmoid colon</td>
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<tr>
<td>Grade of inflammation</td>
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<tr>
<td>1.9 (1.3–2.5)</td>
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<tr>
<td>2.3 (1.2–2.75)</td>
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<td>Collagen layer thickness (µm)</td>
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<tr>
<td>15.3 (7.6–30.3)</td>
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<td>15.6 (8.0–25.5)</td>
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Values are median (range).
No significant differences between groups.

Figure 2 Stool weight [A] and stool frequency [B] before and after eight weeks of therapy with budesonide or placebo.
selection bias, so called “systematically random sampling”.

Figure 4

The thickness of the collagen layer and the grade of inflammation between the results of the two pathologists concerning considered statistically significant. In order to assess the variation and within groups where appropriate; p values <0.05 were used to compare data between Fisher’s exact test, the Wilcoxon test for pair differences, and the Spearman rho test were used to compare data between

Statistical analysis

Fisher’s exact test, the Wilcoxon test for pair differences, and the Spearman rho test were used to compare data between and within groups where appropriate; p values <0.05 were considered statistically significant. In order to assess the variation between the results of the two pathologists concerning the thickness of the collagen layer and the grade of inflammation, the variation coefficient between the results of the two observers was calculated.

RESULTS

Ten patients were randomised to budesonide treatment and 10 patients to placebo treatment. Clinical and histological baseline characteristics were similar in both groups (table 1). All 10 patients who received budesonide had a reduction in stool frequency and/or stool weight of more than 50% whereas only two patients on placebo had a similar response (p<0.001). Median stool frequency was reduced from 6.2 (range 2.7–7.3) per day to 1.9 (range 1.0–3.3) per day in the budesonide group and from 4.5 (range 2.3–7.0) per day to 2.8 (range 2.0–9.0) per day in the placebo group. All patients had daily stool weights above 200 g before treatment. In the budesonide group stool weight was reduced in all 10 patients, in seven patients by more than 50%. Median stool weight was reduced from 574 g/day (range 241–853) to 200 g/day (range 151–346). In the placebo group, seven patients had their daily stool weight measured after treatment; none of these patients had a reduction of more than 50%. The change in median was from 463 g/day (range 229–1280) to 475 g/day (range 232–1084) (fig 2). Two patients refused to perform another faecal sampling after treatment, and the third patient had a volume more than 500 g/day but the exact volume was not measured.

The grade of inflammation at entry was less pronounced in the rectum (median 1.3 (range 0.5–3.0) than in the sigmoid colon (median 2.3 (range 1.3–3.0)) and the median collagen layer was thinner (rectum 9.7 µm (range 4.7–15.4), sigmoid colon 15.6 µm (range 8.0–25.5)). In 11 patients the subepithelial collagen layer in the rectum was less than 10 µm. In the sigmoid colon the median inflammation grade was reduced from 2.3 (range 1.5–2.75) to 1.0 (range 0.0–1.25) (p<0.01) in the budesonide group whereas no significant change was detected in the placebo group (1.9 (range 1.0–2.5) to 1.5 (range 1.0–2.5); NS) (fig 3). The collagen layer in the sigmoid colon was reduced after treatment in the budesonide group (median 15.6 µm (range 8.0–25.5) to 10.2 µm (range 6.1–13.3); p<0.02) but not in the placebo group (median 15.3 µm (range 7.6–30.3) to 12.7 µm (range 8.8–19.7); NS). The grade of inflammation in the sigmoid colon and stool weight correlated significantly (rho=0.53; p<0.001), and a positive correlation between the thickness of the collagen layer and stool weight (rho=0.34; p<0.05) was also found (fig 4). In the rectum, the effect of budesonide was less pronounced and no significant effect on grade of inflammation or collagen layer thickness was detected. However, a positive correlation between rectal collagen layer thickness and stool weight (rho=0.37; p<0.05) but not between grade of inflammation and stool weight (rho=0.27; NS) was found in the rectum.

No systematic difference between the measurements of the two pathologists was observed. The variation coefficient was 0.19 concerning measurement of the thickness of the collagen layer and 0.17 for determination of the grade of inflammation.

Figure 4

[A] Correlation between grade of inflammation in the sigmoid colon and stool weight. Rho <0.531, p<0.001, n=36. [B] Correlation between thickness of the collagen layer in the sigmoid colon and stool weight. Rho <0.337, p<0.05, n=36.
DISCUSSION
This study demonstrates that budesonide has an excellent effect on the clinical symptoms of collagenous colitis. This is in accordance with previous open studies and a recently published placebo controlled trial. Collagenous colitis is characterised by watery diarrhoea and in the present study up to 10 bowel movements a day were found. In most cases the disease has a chronic course with continuous or relapsing symptoms, and the average symptom duration in our study was 9.3 years. We found a reduction in stool frequency and stool weight. Patients with collagenous colitis generally suffer little morbidity but diarrhoea affects daily living. Improvement in clinical symptoms therefore is of great importance and in our study all patients treated with budesonide reported subjective improvement. Quality of life parameters were not assessed in this study but we would recommend this in the future.

In a previous uncontrolled study the effect of prednisolone treatment was evaluated, and treatment was associated with a decrease in stool frequency. However, the effect was transitory and diarrhoea recurred when treatment was discontinued or the dose reduced. Treatment with prednisolone for prolonged periods of time has been recommended but the risk of serious side effects must be recognised.

Budesonide has a topical effect and low systemic activity because of a high first pass metabolism in the liver. Therefore, the risk of corticosteroid associated side effects should be reduced. In a previous study of patients with Crohn's disease, budesonide was compared with prednisolone. Budesonide had fewer corticosteroid related side effects and less effect on adrenal function. Corticosteroid related side effects were not reported in our study and the 9 mg dose of budesonide has been found to be safe in previous studies. Cases of prednisolone refractory collagenous colitis successfully treated with budesonide have been described. Budesonide has a high receptor binding affinity and an enhanced retention time in the mucosa compared with prednisolone and this could be the explanation for a better anti-inflammatory effect of budesonide in collagenous colitis.

Symptoms rapidly return when medication is stopped. In our study, 8/10 patients had relapse of clinical symptoms within eight weeks after withdrawal of budesonide treatment. Most patients may need sustained treatment to remain symptom free and the effect of maintenance treatment with budesonide in patients with collagenous colitis should be studied further. Duration of treatment has to be determined and the long term effects of continuous budesonide treatment should also be studied.

In the normal colonic mucosa the subepithelial collagen band varies from 3 to 6 µm whereas collagenous colitis is characterised by a thickened subepithelial layer and inflammatory infiltrate. The collagen band varies in thickness and characterised by a thickened subepithelial layer and inflammatory band varies from 3 to 6 µm and the long term effects of continuous budesonide treatment studied further. Duration of treatment has to be determined. Most patients may need sustained treatment to remain symptom free and the effect of continuous prednisolone treatment with budesonide has been found to be safe in previous studies. Cases of prednisolone refractory collagenous colitis successfully treated with budesonide have been described. Budesonide has a high receptor binding affinity and an enhanced retention time in the mucosa compared with prednisolone and this could be the explanation for a better anti-inflammatory effect of budesonide in collagenous colitis.

In conclusion, we found that budesonide is highly effective and well tolerated in the treatment of collagenous colitis. Effects on both clinical symptoms and inflammatory infiltrate were seen. However, there is a high risk of relapse after stopping eight weeks of treatment.

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REFERENCES