Glucocorticoid treatment in ileal Crohn’s disease: relief of symptoms but not of endoscopically viewed inflammation

G Olaison, R Sjödahl, C Tagesson

Abstract
The effect of prednisolone (20-30 mg daily for six to nine weeks) was studied in eight patients with Crohn’s disease and recurrent, preanastomotic ileal inflammation, in respect of symptoms, endoscopic findings and phospholipase A2 activity in the ileal mucosa. The Harvey-Bradshaw Crohn’s disease activity index improved significantly, mainly because of reduced frequency of loose stools and diminution of abdominal pain. Endoscopy revealed no corresponding decrease in ileal inflammation, which in all cases persisted after treatment. The phospholipase A2 activity in the ileal mucosa was not altered by prednisolone. In two of three patients with concomitant colitis colonic inflammation improved. The study confirmed earlier reports of good symptomatic relief from glucocorticoid treatment in Crohn’s disease of the small bowel, but endoscopy suggests that this improvement was not the result of resolution of small intestinal mucosal inflammation.

Although Crohn’s disease has been recognised for about 50 years, its aetiology remains obscure and the inflammation inducing mechanisms are poorly understood. Phospholipase A2 is implicated as a major contributor to inflammatory processes, and has attracted much attention because of its ability to produce substrate for the generation of various inflammatory lipid mediators. Raised intestinal contents of prostan- landins and leucotrienes have been reported in Crohn’s disease. In line with these findings, we reported increased activity of phospholipase A2 in the ileal mucosa of patients with ileocaecal Crohn’s disease, suggesting a role for this enzyme in the development of the inflammatory process. Glucocorticoids are considered to be inhibitors of phospholipase A2 activity and are among the few drugs with documented effect on Crohn’s disease of the small intestine. These steroids have been stated to exert their anti-inflammatory action by inducing synthesis of a phospholipase A2-inhibiting protein.

In ulcerative colitis prednisolone was found to induce remission of symptoms concomitantly with reduction of endoscopically viewed colonic inflammation. Reports on the effect in Crohn’s colitis are mainly anecdotal, but steroids appear to be beneficial in some cases. Their effect on endoscopically visualised inflammation of the small bowel in Crohn’s disease does not appear in the literature. Nor have we found any report concerning possible influence on the activity of mucosal phospholipase A2.

Fibreoptic gastrointestinal endoscopy offers unique opportunities for the study of the ileal mucosa in Crohn’s disease in vivo and for assessing the effects of different treatments. Mucosal biopsy can also be performed. We have studied the effects of prednisolone treatment in eight patients with Crohn’s disease. All had previously undergone resection and had recurrent preanastomotic ileal inflammation. The patients were assessed before, and also six to nine weeks after medication in regard to symptoms, activity of phospholipase A2 and endoscopic appearance of the preanastomotic ileal mucosa.

Methods
Patients
Eight patients with Crohn’s disease were studied aged 20–61 years (mean 43). Ileocaecal resection with anastomosis of ileum to ascending colon had previously been performed in six cases and colectomy with ileorectal anastomosis (for Crohn’s colitis) in two. Ileocolonoscopy in all cases showed recurrent inflammation located preanastomotically in the neoterminal ileum. Three patients had at endoscopy concomitant colitis. Radiographic investigations before the study revealed no additional Crohn’s lesions in the small intestine. The diagnosis of Crohn’s disease was based on classic radiographic findings and the Morson criteria for histopathology of the previously resected tissue.

Endoscopy
Ileocolonoscopy was performed by one of the authors (GO), using an Olympus CR-101 or CF-IBW colonoscope. The rectum, the remaining colon, the ileocolic or ileorectal anastomosis and, when possible, the distal part of the neoterminal ileum were inspected. In reporting the observations, 1.5 cm of the neoterminal ileum from the junction of the ileal and colonic mucosa was referred to as the ‘anastomosis’ and the ileum proximal thereto was the ‘ileum’. The presence of oedema, erythema, ulcers and stricture was assessed. Ulcers were denoted as aphthous, width less than 4 mm or width 4 mm or more. Strictures were classified as 4–8 mm or less than 4 mm. In assessing the width of anastomoses and the size of ulcers, an open biopsy forceps (width 8 mm) was used for comparison. Ulcer size was measured at the largest diameter, and no attempt was made to quantify depth of ulcers. Erythema was assessed by comparing different parts of the intestine. Oedema was subjectively graded by the investigator.
Biopsy specimens for enzyme analysis were taken from the neoterminal ileum 1–3 cm above the ileocolic anastomosis. To confirm correct visualisation of the site of anastomosis, specimens for light microscopy were taken immediately above and below the mucosal join.

STUDY DESIGN
Before the study all patients underwent thorough clinical examination and ileocolonoscopy, when mucosal biopsies were made for enzyme analysis. The activity of Crohn's disease was assessed according to the Crohn's disease activity index proposed by Harvey and Bradshaw18 (Table I), based only on symptoms. Values of 4–7 were classified as moderately severe, and higher figures as severe.

Glucocorticoid (prednisolone) medication was begun with 30 mg daily for two weeks, followed by 25 mg/day for two weeks, and thereafter 20 mg/day. After six to nine weeks, while still on treatment, the patients were re-examined.

PHOSPHOLIPASE A₂ ANALYSIS
The biopsy specimens were frozen at −70°C until analysis. They were then thawed, weighed, and disintegrated in a Dounce homogeniser, using 0.15 mol NaCl as homogenising medium. Phospholipase A₂ activity was assayed using radiolabelled Escherichia coli as described previously.19 The reaction mixture (final volume 450 μl) contained radiolabelled Escherichia coli (10¹⁰ cpm), 70 mmol Tris-HCl buffer, pH 6.0, 2 mmol CaCl₂ and mucosal cells corresponding to 10 μg protein. The mixture was incubated at 37°C for 90 minutes and the reaction was stopped by adding 2 ml cold 0.15 mol NaCl with 1% bovine serum albumin.

The suspension was then passed through an 0.45 μm millipore filter (Millex SFHA 025 BO, Millipore, Y Frölunda, Sweden), and the radioactivity in the filtrate was counted and expressed in percentage of total radioactivity. One unit of enzyme activity was defined as liberation of 1% of the total radioactivity into the millipore filtrate.

STATISTICAL ANALYSIS
All values are expressed as means ± standard deviation (SD). Two-tailed Wilcoxon's test for paired comparison was used, and p<0.05 was considered statistically significant. The study was approved by the local Committee on Ethics.

Results
Glucocorticoid treatment had good subjective effect in all eight patients, with significant (p<0.01) improvement of symptoms according to the Harvey-Bradshaw activity index (Table II). Clinical remission occurred in two of the three patients with moderately severe symptoms at the start of treatment. The other five patients had severe symptoms, which could be reclassified as moderate in three and remitted in two. Reduction of the symptom index was mainly the result of significantly fewer (p<0.02) loose stools in all eight patients. Of the seven patients who reported abdominal pain, five had improved after the treatment.

Pretreatment endoscopy revealed inflammatory changes in the anastomotic area in all eight patients (Table III). In all the patients without generalised colitis-proctitis, the anastomotic recurrence was located on the ileal side of the anastomosis. Ulcers rarely bridge the mucosal join over to the colonic side. Erythema was strictly confined to the ileal side of the anastomosis.

Post treatment endoscopy showed improvement of the inflammatory state of the ileum in two patients (disappearance of erythema or aphthous ulcers). At the anastomosis the inflammation generally was more pronounced with ulcers in seven cases and stricture in four. In one case a tight stricture widened to more than 4 mm (diminution of ulcers) and another deteriorated from more to less than 4 mm (diminution of ulcer but narrowing of the anastomosis, probably cicatrical). Slight endoscopic improvement of anastomotic inflammation — reduction of ulcer size and of oedema — was observed in five other patients, but was insufficient to change the classification according to ulcer size. In two patients whose first endoscopy showed extensive coloproctitis there was complete healing after prednisolone treatment.

No correlation was found between presence of abdominal pain and anastomotic stricture or between relief of pain and regression of such stricture. Five of the seven patients with abdominal pain reported improvement after prednisolone treatment. Three of the five had no stricture and two had unchanged stricture. Of the two patients with unchanged abdominal pain, one had reduction of stricture.

The mucosal phospholipase A₂ activity in the

<table>
<thead>
<tr>
<th>Disease activity index</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Significance of difference (p-values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(see Table I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge activity</td>
<td>10.9 (4.1)</td>
<td>3.6 (1.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Loose stools/day</td>
<td>7.8 (3.2)</td>
<td>2.9 (1.5)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>(see Table I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6 (1.0)</td>
<td>2.5 (1.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Phospholipase A₂ activity (units)</td>
<td>33.0 (6.6)</td>
<td>32.6 (4.5)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
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Table III  Effects of long-term prednisolone treatment on endoscopic findings in eight cases of Crohn's disease with previous bowel resection and recurrent anastomotic inflammation

<table>
<thead>
<tr>
<th>Endoscopic lesions</th>
<th>Ileum</th>
<th>Anastomosis</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before prednisolone</td>
<td>After prednisolone</td>
<td>Before prednisolone</td>
</tr>
<tr>
<td>Erytema present</td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Erytema absent</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Not visualised</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>No ulceration</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Aphthous ulceration</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ulcers &lt; 4 mm</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Ulcers &gt; 4 mm</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Not visualised</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Stricture absent</td>
<td>6</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Stricture &lt; 4 mm</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Not visualised</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

The treatment period before reinvestigation was only six to nine weeks in our cases, and it is not unlikely that more extensive healing would have been found after longer medication. Moreover, it cannot be excluded that healing starts in areas of the gut that are too proximal or too deep in the intestinal wall for endoscopic visualisation.

The mucosal phospholipase A2 activity in the neoterminal ileum was not inhibited by glucocorticoid medication. The implications of this observation are not clear. The unaffected phospholipase A2 activity in biopsy specimens of superficial ileal mucosa accorded with substantially unchanged inflammation at endoscopic viewing. It seems noteworthy that our patients had chronic inflammation and were receiving longterm prednisolone, whereas experimental studies showing induction of phospholipase inhibition by glucocorticoids were short term and performed on non-human tissues. Moreover recent investigations have questioned the mechanism by which glucocorticoids inhibits phospholipase A2 activity, and our data further question the phospholipase A2 inhibitory effect by glucocorticoids.

Our study thus confirmed the excellent effect of glucocorticoids on symptoms of Crohn's disease of the small intestine but this, remarkably, was not accompanied by a significant diminution of endoscopically observed small intestinal inflammation. These findings suggest that at least some of the symptoms in small bowel Crohn's disease are not caused by the mucosal endoscopically visualised inflammation, but by other, concomitant factors.

This study was aided by grants from Ostergrunds County Council, The Swedish Society of Medicine, The Swedish Society of Medical Research and by grant B 88-17X-00983-006 from the Swedish Medical Research Council.

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Gut 1990 31: 325-328
doi: 10.1136/gut.31.3.325