Double-Blind Comparison of Slow-Release 5-Aminosalicylate and Sulfasalazine in Remission Maintenance in Ulcerative Colitis

CHRIS J. J. MULDER, GUIDO N. J. TYTGAT, IRENE T. WETERMAN, WILLEM DEKKER, PAUL BLOK, MAX SCHRIJVER, and HERBERT V. N. HEIDE

Department of Gastroenterology-Hepatology, Academic Medical Center, Amsterdam; Department of Gastroenterology, Academic Hospital, Leiden; Department of Gastroenterology, Elisabeth Gasthuis, Haarlem; Department of Pathology, Municipal Medical and Health Center, Haarlem; and Department of Internal Medicine, Bronovo Hospital, The Hague, the Netherlands

The results of a clinical trial comparing slow-release 5-aminosalicylic acid tablets (Pentasa) and enteric-coated sulfasalazine tablets (Salazopyrin) with regard to the efficacy of maintaining ulcerative colitis patients in remission for 12 mo and with regard to safety of treatment are reported. Seventy-five patients with ulcerative colitis in remission for between 1 mo and 5 yr were included for analysis. Forty-nine men and 26 women, aged between 18 and 79 yr, received either Pentasa t.i.d. (1500 mg) plus Salazopyrin placebo or Salazopyrin t.i.d. (3 g) plus Pentasa placebo daily. Patients were assessed clinically, endoscopically, and histologically before and 3, 6, 9, and 12 mo after the start of treatment. Life-table analysis showed ongoing remission after 6 and 12 mo for Pentasa to be 63% (26 of 41) and 54% (22 of 41) and for Salazopyrin 72% (22 of 31) and 46% (14 of 31). These differences were not statistically significant. Three patients treated with Salazopyrin were withdrawn because of severe erythrodermia, anxiety and backache, and pregnancy, respectively. One patient on Salazopyrin experienced transient rises in serum urea, creatinine, and lactic dehydrogenase and another patient in this group reported slight reversible loss of hair. In the Pentasa group no side effects were recorded. We conclude that Pentasa is a well-tolerated drug, equally effective as Salazopyrin in maintenance of remission of ulcerative colitis.

The natural history of ulcerative colitis (UC) is characterized by periods of remission interspersed with exacerbations. The aim of therapy is to keep the condition of the patient stable, maintaining remission whenever possible.

Sulfasalazine (salicylazosulfapyridine) has been shown to be effective in treating acute attacks of UC (1,2) and also in maintaining remission (3–5). However, tolerance to the drug is often poor (6). Sulfasalazine consists of sulfapyridine and 5-aminosalicylic acid (5-ASA) joined by an azo-bond, which is split by bacteria in the colon, releasing the constituents. The sulfapyridine moiety is now known to cause the majority of the adverse reactions of sulfasalazine, including allergy, whereas the 5-ASA moiety has been shown to be the active component in inflammatory bowel disease (7–11). The latter drug has been investigated in oral, enema, and suppository forms in active colitis and in refractory proctitis (7–14). 5-Aminosalicylic acid cannot be given by mouth as it is unstable in acid and is rapidly absorbed by the small intestine. Delivery systems have been developed to bypass this problem.

The Pentasa tablets used in this study have been designed to release 5-ASA slowly and in a pH-dependent way. Part of the active substance is released and about a third absorbed in the small intestine; therefore, the majority is available for activity in the distal ileum and colon (15,16). 5-Aminosalicylic acid coated with an acrylic-based resin has been tested for maintenance therapy in UC (17,18).
Until now clinical experience with Pentasa tablets has been limited to small groups of patients. This study was designed to compare the efficacy and safety of 5-ASA acid microgranules coated with a semipermeable membrane of ethyl cellulose (Pentasa) with sulfasalazine for maintenance of remission in UC.

Materials and Methods

Study Design

This study was designed as a double-blind, double-dummy, randomized multicenter study. The aim was to compare the efficacy of 12 mo of treatment with slow-release 5-ASA tablets (Pentasa) and sulfasalazine enteric-coated tablets (Salazopyrin E.C) in preventing relapse in patients with UC in remission and to compare the incidence of side effects and the tolerance to these two treatments. Ulcerative colitis was diagnosed by assessing the usual clinical, endoscopic, and histologic criteria (19–21).

The study was conducted under the provisions of the Declaration of Helsinki.

Patients

Male and female outpatients, aged ≥18 yr, with UC in remission for between 1 mo and 5 yr who had not taken steroids (either orally or as an enema) or azathioprine during at least 1 mo before entry were included. Excluded were all pregnant and lactating women, women of childbearing potential not taking adequate contraceptive measures, patients who were likely to be unreliable to follow the instructions properly, patients allergic to aspirin, other salicylates, or sulfonamides, patients with malignant disease, and patients with renal disease, especially those with analgesic nephritis.

Randomization

According to a double-blind randomization code, patients were either allocated to treatment with active Pentasa tablets + placebo Salazopyrin E.C tablets or to placebo Pentasa tablets + active Salazopyrin E.C tablets.

Medication

Patients received either 6 tablets (1500 mg) of Pentasa plus 6 placebo tablets of Salazopyrin E.C or 6 placebo tablets of Pentasa plus 6 tablets (3 g) of Salazopyrin E.C daily. The patients were instructed to take their daily dosage in three doses before or after the main meals. The duration of treatment was 12 mo.

The placebo tablets were identical in appearance, weight, and taste.

Assessments

Before the start of the study, all relevant medical and family history data were noted, including symptoms, duration of disease, previous therapy, response to previous therapy, allergy, and all other (concomitant) therapy previously taken by the patient. Patients were assessed clinically, endoscopically (recto/sigmoidoscopy) (20), and histologically (21) before and in remission for between 1 mo and 5 yr after the start of treatment. At endoscopy the mucosal color, vessel pattern, granularity, presence of valves, distention, polypoid structures, ulcers, spontaneous hemorrhage, and mucopurulent covering were studied and a wipe-test was performed to determine friability. Overall, endoscopy was scored from normal through mild, moderate, and severe abnormality to very severe abnormality.

As for histology, the biopsy specimens were examined for edema and hemorrhage in the mucosa and submucosa, for quality and quantity of mucosal cellular infiltrate, and for epithelial architecture of the crypts. They were finally scored as normal, little inflammation, medium inflammation, severe inflammation, or UC in remission. Patients were assessed immediately if symptoms developed or if side effects occurred.

After the completion of the study it was to be determined whether a patient had remained in remission or not. The following criteria were used to assess this:

If all the data obtained at each visit were assessed as "normal" or "in remission," the patient was considered to have remained in remission.

If at any time during the study all the data obtained were not considered to be "normal" or "in remission" or if the investigator had given a prescription for additional treatment (e.g., enemas), then the patient was considered to have experienced relapse.

In case of abnormalities in only one or two of the assessment groups (clinical, endoscopic, histologic), the patient’s data were discussed by the monitor with a blinded investigator. In this way a final judgment as to whether the patient had remained in remission or not was given.

Relevant laboratory data were obtained during every visit [erythrocyte sedimentation rate, hemoglobin, hematocrit, leukocytes, thrombocytes, albumin, alkaline phosphatase, total protein, γ-glutamyl transaminase, urea, creatinine, lactate dehydrogenase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and urine (protein, glucose, and sediment)]. During each visit the patients were asked whether any unusual event had occurred during the preceding period. The patients were not asked for specific signs or symptoms. Side effects were recorded on special forms.

Statistics

Before evaluating the results of therapy, it was checked whether the groups were comparable per treatment and per center. This was done using analysis of variance, Student’s t-test, χ² tests, Fisher’s test (two-sided), and Mantel–Haenszel χ² tests where appropriate. The data concerning the remission rates were statistically evaluated using life-table analysis with the SAS statistical package and the log-rank test was applied to detect significant differences.
Table 1. Initial Patient Data

<table>
<thead>
<tr>
<th></th>
<th>Pentasa</th>
<th>Salazopyrin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>41</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>29/12</td>
<td>20/14</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (yr)</td>
<td>43.3 ± 15.6</td>
<td>42.0 ± 11.5</td>
<td></td>
</tr>
<tr>
<td>Range (yr)</td>
<td>18-79</td>
<td>22-63</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (yr)</td>
<td>9.7 ± 10.2</td>
<td>9.5 ± 8.4</td>
<td></td>
</tr>
<tr>
<td>Range (yr)</td>
<td>0.5 ± 42</td>
<td>0.4 ± 40</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of remission before the trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (mo)</td>
<td>13.6 ± 13.8</td>
<td>10.6 ± 10.1</td>
<td>NS</td>
</tr>
<tr>
<td>Range (mo)</td>
<td>1-46</td>
<td>2-39</td>
<td></td>
</tr>
<tr>
<td>Median (mo)</td>
<td>7</td>
<td>7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Proctosigmoiditis</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Pancolitis</td>
<td>8</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Salazopyrin therapy during month before entry (n)</td>
<td>40</td>
<td>33</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.

Results

Dropouts

Three patients dropped out of the study before the first follow-up visit. One patient (Salazopyrin) considered the tablets unpalatable and 2 patients stopped the therapy because of lack of motivation (Pentasa 1, Salazopyrin 1). Dropouts were not included in the analysis.

Protocol Violations

Six patients on Pentasa and 6 patients on Salazopyrin did not fulfill the inclusion criteria: they had not been in complete remission at least 1 mo before entry into the study. These patients were only included in the safety analysis.

Patients

Seventy-five patients, 49 men and 26 women, with ages ranging from 18 to 79 yr were available for analysis. Forty-one were treated with Pentasa and 34 with Salazopyrin. Eight of the 41 patients in the Pentasa group stopped the trial medication after they had experienced a relapse, despite the investigator's request to continue. Four patients in the Salazopyrin group did the same. Another 3 patients in the Salazopyrin group were withdrawn: one developed severe erythrodermia 5 wk after the start of treatment, another complained of anxiety and backache 6 wk after the start of treatment, and the third left the study after 3 mo of therapy because of pregnancy (a healthy baby was born), but she continued open Salazopyrin therapy.

Patient Characteristics

Both groups were comparable for all parameters per treatment and per center. All except 2 patients had been on sulfasalazine before the study (Table 1).

Evaluation of Efficacy in Maintaining Remission

The data of 41 patients treated with Pentasa and 34 patients treated with Salazopyrin in four centers were included in the life-table analysis for calculating the remission rates. The results are shown in Figure 1. No significant differences between the two treatments were revealed ($\chi^2 = 0.14$, df = 1, $p > 0.70$). The final remission rates were 54% for Pentasa and 46% for Salazopyrin, with 95% confidence intervals of 38%–69% for Pentasa and 29%–64% for Salazopyrin. The difference is 8% in favor of Pentasa, with a 95% confidence interval of +16% to +31%.

Safety Analysis

Laboratory findings. One patient on Pentasa had transient slight abnormalities in the urinary sediment (bacteria, leukocytes, and erythrocytes) at 3 and 9 mo. One patient on Salazopyrin had a transient rise in serum urea, creatinine, and lactic dehydrogenase after 3 mo of therapy. Eighteen days later the values were normalized. The possibility of a laboratory error was considered.

Tolerance. One patient on Salazopyrin dropped out almost immediately because she thought the tablets were unpalatable. Two patients receiving Salazopyrin, one developing severe erythrodermia and another anxiety/backache, were dis...
cussed above as withdrawals. Another patient on Salazopyrin reported slight loss of hair during the treatment, which seemed to recover after treatment was stopped.

Discussion

No statistically significant differences were revealed between Pentasa and Salazopyrin with respect to their ability to maintain remission in UC. There was a slight trend in favor of Pentasa as it maintained remission in 54% of patients over the year whereas the figure for Salazopyrin was 46%.

Several studies have been published showing that 5-ASA, when delivered to the colon in a suitable form, is effective in UC (16). This study not only provides additional evidence of 5-ASA being the active moiety of sulfasalazine but also demonstrates that, when given in the Pentasa slow-release preparation, it is at least as effective as the "parent drug.

It has already been argued that Pentasa, on theoretical grounds, should constitute an advance with regard to tolerance. Should adverse reactions be observed they will in all likelihood be limited to those ascribed to the salicylates in general. The rate at which the patient is able to acetylate absorbed 5-ASA may play a major part in the frequency and severity of side effects. In this study Pentasa lived up to expectations as no adverse reactions were recorded. In contrast, 3 patients in the Salazopyrin group suffered side effects. Hair loss during Salazopyrin therapy was recently reported by others too (22). One patient in our study had to be withdrawn because of severe erythrodermia. It is well known that sulfasalazine can cause reactions necessitating discontinuation of therapy (6).

In this study we did not monitor plasma levels or urinary excretion of 5-ASA or its main metabolite acetyl-5-ASA. However, a Danish group recently published the results of Pentasa and Salazopyrin urine and plasma level determinations in patients with UC and Crohn's disease (23,24). Although these studies do not involve a direct comparison of similar patient groups, we believe that it can be concluded that 1.5 g/day Pentasa is probably as safe as Salazopyrin as far as the 5-ASA moiety is concerned.

This study shows that Pentasa is another promising slow-release 5-ASA preparation, equally effective in maintaining remission in colitis and therefore especially useful in patients unable to take sulfasalazine (25).

References