Healing of Chronic Antral Gastritis: Effect of Sucralfate and Colloidal Bismuth Subcitrate

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Abstract

Background: Colloidal bismuth subcitrate (CBS) causes endoscopic and histological improvement in gastritis and eradication of Helicobacter pylori in patients with non-ulcer dyspepsia (NUD). The effect of sucralfate, a cytoprotective drug, on endoscopic and histologic gastritis and H pylori clearance is not clear. We studied the effect of CBS and sucralfate on these features in patients with NUD.

Methods: Sixty three patients with NUD and H pylori infection were randomized to receive one of the following for four weeks: (i) CBS (240 mg twice daily) (Group 1); (ii) placebo I, similar in size, color and shape to CBS (Group 2); (iii) sucralfate (2.0 g twice daily) (Group 3) and (iv) placebo II, similar to sucralfate (Group 4). Symptomatic, endoscopic and histological findings and H pylori status were assessed before and after treatment.

Results: Similar symptomatic improvement was observed with each treatment, indicating a placebo effect. Significant endoscopic and histological improvement was observed with CBS only. CBS was better than sucralfate in inducing endoscopic and histological improvement. Clearance rate of H pylori was 46.6% with CBS, 16.6% with its placebo, 33.3% with sucralfate and 13.3% with its placebo.

Conclusion: CBS is more effective than sucralfate in inducing endoscopic and histologic healing of H pylori-related gastritis among NUD patients.

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Key words: Bismuth preparations, gastritis, cytoprotection, Helicobacter pylori, non-ulcer dyspepsia.

Introduction

Non-ulcer dyspepsia (NUD) is a syndrome of uncertain pathogenesis that affects 20% to 30% of the general population. More than 50% of patients have histological chronic antral gastritis even though the mucosa may appear normal endoscopically. However, the relationship of gastritis with symptoms is controversial since similar changes are seen in 50% or more of normal subjects in the fifth decade of life. Since Helicobacter pylori infection has been found to be almost invariably associated with chronic antral gastritis, it is considered to be the cause of gastritis.

Several studies have shown that colloidal bismuth subcitrate (CBS) induces healing of histologic gastritis and suppression or eradication of H pylori in NUD patients. Its effect on symptoms has however been conflicting, varying from significant symptomatic amelioration to results no different from placebo. The improvement seen with CBS has been attributed to its antibacterial action against H pylori. However, CBS also has a cytoprotective action on the gastric mucosa, which may cause improvement of gastritis and hence suppression of H pylori.

Sucralfate is a pure cytoprotective drug which lacks antibacterial activity. It has been shown to induce endoscopic and histologic improvement of chronic antral gastritis. It also reduced the density of H pylori in patients with duodenal ulcer-associated gastritis in one study. Only a few studies have compared the efficacy of CBS and sucralfate in inducing symptomatic relief or in healing of gastritis directly. We therefore decided to undertake such a study.

Methods

Patients with NUD attending our hospital's outpatient services were screened for inclusion in the study. NUD was defined as presence of upper abdominal pain or discomfort for a period of at least four weeks in the absence of gastric or duodenal ulcer(s), reflux esophagitis, active duodenitis, and neoplastic lesions at upper gastrointestinal endoscopy. Patients with the following features were excluded: i) history of duodenal ulcer documented by radiographic contrast study or endoscopy in the past, ii) pain related to defecation, iii) history of receiving non-steroidal anti-inflammatory drugs on a regular basis, iv) history of receiving antibiotics in the previous four weeks, v) evidence of biliary or pancreatic disease on ultrasonography, and vi) pregnant women. Informed consent was obtained from all the patients and
the study was approved by our institution's Ethics Committee.

All patients underwent upper gastroduodenal endoscopy. Endoscopic findings were recorded and gastric antral mucosal biopsies obtained. Biopsy specimens were subjected to rapid urease test, histology and Gram's stain. Those patients who had the urease test and at least one of the other two tests positive for the presence of *H pylori* were included in the study. One biopsy specimen was subjected to culture for *H pylori* though the results of this were not taken into consideration before randomization for treatment.

Study patients were randomized by an opaque envelope method to receive two tablets twice daily of one of the following for four weeks: (i) CBS (120 mg per tablet) (Group 1); (ii) placebo I, similar in size, color and shape to CBS (Group 2); (iii) sucralfate (1.0 g per tablet) (Group 3), and (iv) placebo II, similar to sucralfate (Group 4). All the patients underwent symptomatic, endoscopic and histologic assessment before and 2-3 weeks after treatment.

**Symptom assessment**

Symptoms were scored using a weighted scale which has been used previously. The minimum and maximum possible scores on this scale were 0 and 18, respectively.

**Endoscopy and histology**

After an overnight fast, patients underwent upper gastrointestinal endoscopy without any anesthesia or premedication. Each anatomical region of the stomach (i.e. fundus, body, greater curve, lesser curve and antrum) and duodenum was examined and endoscopic changes were graded using a semi-quantitative scoring system; the minimum possible score was 0 and the maximum 17. Multiple biopsy pieces were obtained from the antrum for urease test (one piece), Gram staining (one piece), culture for *H pylori* (one piece), and histological examination (two to three pieces).

We used a modification of a rapid urease test described previously, in this, a gastric mucosal biopsy specimen was immediately inoculated into the rapid urease medium and observed periodically for 20 minutes for change of color from yellow to pink. Two pieces were transported to the laboratory in 0.2 ml of Columbia broth (Difco Laboratories, USA) for smear examination and culture. Impression and crushed smears were prepared from one of these pieces on clean glass slides and stained with modified Gram method using dilute carbol fuchsin as counterstain. The smears were examined under an oil immersion lens (X 1000) for typical spiral, curved, Gram-negative bacteria. The other biopsy piece was homogenized in a glass tissue homogenizer and 2-3 loopfuls of the tissue homogenate were inoculated on sheep chocolate agar (Columbia agar base with 10% sheep blood; Difco) containing the following antibiotics: ampicillin B 2 mg/L, vancomycin 6 mg/L and poly-mixin B 2500 units/L. The plates were incubated at 37°C under microaerophilic conditions using a candle jar technique, and were examined after 3, 5 and 7 days of inoculation. Characteristic colonies were identified by Gram staining, motility and biochemical tests including catalase, oxidase and urease positivity.

Biopsy specimens for histology were fixed in 10% formaldehyde, embedded in paraffin and serially sectioned at 5 μm thickness. The sections were stained with hematoxylin and eosin (H & E), Giemsa and Warthin-Starry technique, and examined by a histopathologist who was not aware of clinical or endoscopic findings. As with endoscopy, histological findings were scored using a previously-described scoring system: the minimum and maximum possible scores were 0 and 39, respectively.

Clearance of *H pylori* was defined as failure to detect the presence of the organism on all the four tests used, namely, rapid urease test, Gram's stain, histology and culture.

**Statistical methods**

Intragroup and intergroup comparisons of symptomatic, endoscopic and histological scores were done using Wilcoxon's signed rank test and Wilcoxon's rank sum test respectively at an alpha level of 0.05 (two-tailed). The rates of clearance of *H pylori* in different groups were compared using the chi-squared test.

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**Table 1: Symptom, endoscopic and histological scores before and after each treatment.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score before treatment</th>
<th>Score after treatment</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>9 (5-13)</td>
<td>5 (7-8)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Group 2</td>
<td>8 (5-12)</td>
<td>6 (3-10)</td>
<td>0.001</td>
</tr>
<tr>
<td>Group 3</td>
<td>8 (5-14)</td>
<td>6 (2-13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Group 4</td>
<td>6 (5-15)</td>
<td>6 (0-14)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Endoscopic scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>2 (0-5)</td>
<td>1 (0-3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Group 2</td>
<td>2 (0-6)</td>
<td>1 (0-4)</td>
<td>NS</td>
</tr>
<tr>
<td>Group 3</td>
<td>1 (0-3)</td>
<td>1 (1-6)</td>
<td>NS</td>
</tr>
<tr>
<td>Group 4</td>
<td>1 (0-4)</td>
<td>0 (0-4)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Histological scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>9 (5-15)</td>
<td>6 (4-12)</td>
<td>0.003</td>
</tr>
<tr>
<td>Group 2</td>
<td>8 (5-15)</td>
<td>9 (4-14)</td>
<td>NS</td>
</tr>
<tr>
<td>Group 3</td>
<td>8 (2-14)</td>
<td>9 (2-15)</td>
<td>NS</td>
</tr>
<tr>
<td>Group 4</td>
<td>7 (2-11)</td>
<td>7 (2-16)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*All data are shown as median [range]; NS = not significant; *= Wilcoxon's signed rank test.
Results
Eighty-one patients were enrolled in the study. Eighteen patients dropped out and sixty-three completed the study. The number of patients in each group and their mean age (± SD) and sex distribution were as follows: Group 1: 18 (age 30.2 ± 8.1 y, 10 men), Group 2: 15 (32.0 ± 11.7 y, 14 men), Group 3: 15 (29.0 ± 6.4 y, 7 men) and Group 4: 15 (29.2 ± 7.2 y, 11 men). Culture was positive in only 16 (23%) patients.

Symptomatic, endoscopic and histological scores before and after treatment are shown in Table 1. Significant symptomatic improvement was observed in all groups indicating a placebo effect (Figs 1 and 2). Both CBS and sucralfate showed symptomatic improvement comparable to their respective placebos and to each other.

Significant endoscopic and histological improvement was observed only in the CBS group (Figs 1 and 2). CBS was better than sucralfate in inducing endoscopic and histological improvement (Table 2).

Clearance rates of *H pylori* after 4 weeks of therapy were 7/15 (46.6%) with CBS, 3/18 (16.6%) with its placebo, 5/15 (33.3%) with sucralfate and 2/15 (13.3%) with its placebo. There was no significant difference between these groups. When the two placebo groups were combined together, a significant difference (χ² = 3.91, p < 0.05) was observed with CBS but not with sucralfate.

Discussion
Our data show that CBS was more effective than sucralfate in inducing healing of endoscopic and histologic gastritis. It also cleared *H pylori* in nearly half the patients. Symptomatic improvement with both CBS and sucralfate was however similar to each other and also to their respective placebos.

CBS has both bactericidal activity against *H pylori* and a cytoprotective action on gastric mucosa. Sucralfate, on the other hand, has only a cytoprotective action and does not have in vitro or in vivo activity against *H pylori*. In an animal study, CBS was shown to have a more potent cytoprotective action than sucralfate on a weight basis. In the dosages used in our study, CBS was expected to have a bacteriostatic effect and the two drugs were expected to have approximately equal cytoprotective efficacy. In a recent study, sucralfate-treated duodenal ulcer patients had more marked improvement of associated antral gastritis and more marked reduction in density of *H pylori* as compared to those treated with cimetidine. However, in another study, eradication of *H pylori* with a combination of sucralfate, thiazole and tetracycline was no better than that with ranitidine alone. In our study, CBS was better than sucralfate in inducing endoscopic and histological improvement.

In a study design somewhat similar to ours, Rauws

| Table 2: Intergroup comparisons of changes in symptom, endoscopic and histological scores with treatment |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Group  | Group  | Group  |
| 1 vs 2 | 3 vs 4 | 1 vs 3 |
| Symptom scores | NS  | NS  | NS  |
| Endoscopic scores | NS  | NS  | 0.007 |
| Histological scores | NS  | NS  | 0.002 |

All data are shown as *p* values; NS = not significant.

NON-ULCER DYSPEPSIA: BISMUTH VS SUCRALKATE

- KUMAR ET AL.
also reported that patients with NUD improved their gastritis score and eradicated *H pylori* infection with CBS, amoxycillin and a combination of these two drugs but not with sucralfate, cimetidine or a placebo. Our results of better endoscopic and histologic healing with CBS support these findings.

Reports on the effect of CBS on symptoms in patients with NUD and chronic antral gastritis with or without *H pylori* infection are however conflicting. In our study, though CBS in a dosage of 240 mg twice a day led to endoscopic and histological improvement in gastritis and eradication of *H pylori*, it did not improve symptoms. Our results thus are similar to those of other studies which showed no effect of CBS on symptoms in spite of improvement in gastritis and eradication of *H pylori*. It is however possible that this lack of symptomatic improvement may owe to a short duration of treatment.

References