Campylobacter associated gastritis in patients with non-ulcer dyspepsia: a double blind placebo controlled trial with colloidal bismuth subcitrate

R J L F Loffeld, H V J P Potters, E Stobberingh, J A Flendrig, J P Van Spreeuwel, and J W Arends

From the Departments of Internal Medicine, Pathology, and Medical Microbiology, University Hospital Maastricht, and the Department of Pathology, Bleuland Hospital, Gouda, The Netherlands

SUMMARY Fifty consecutive patients with non-ulcer dyspepsia and a Campylobacter associated gastritis (CAG) were randomly assigned to treatment with colloidal bismuth subcitrate (CBS) 240 mg twice daily or placebo, according to a double blind study design. After the blind treatment an ‘open’ treatment with CBS was started in both groups. Twenty six patients treated with CBS showed a significant reduction in colonisation with Campylobacter pylori and a significant improvement in the Whitehead gastritis score. No significant changes were recorded in twenty four patients treated with placebo. After an additional course of CBS no further improvement in gastritis score was noted but there was a further reduction in Campylobacter colonisation. CBS did not greatly alter subjective complaints. Subjective complaints were improved in both treatment groups except for nausea and meteorism that improved more in the CBS treated patients. This finding again questions the clinical significance of gastritis and also casts doubt on the clinical relevance of therapeutical measures aimed at eradication of C pylori.

Reports on the presence of spiral bacteria in the human stomach have appeared sporadically over the last century.1-3 Since the work of Marshall and Warren, however, the possible pathogenetic significance of these organisms on type B (antral) gastritis was appreciated,4 and was confirmed by other investigators.5-6 Campylobacter pylori is found in 98% of patients with gastritis, in 80% of patients with gastric ulcer and in 90% of patients with duodenal ulcers. In patients with dyspeptic symptoms but normal gastric histology C pylori has also been seen overlying the mucosa but only in small numbers.5 About one third of patients referred for upper gastrointestinal endoscopy because of upper abdominal complaints appear not to suffer from peptic ulcers, oesophagitis, active duodenitis, or gastric carcinoma and therefore by definition suffer from so-called non-ulcer dyspepsia. These patients constitute a heterogeneous group for which at present no effective therapy is available. It has been shown that more than half of the patients with non-ulcer dyspepsia histologically show an active chronic gastritis.6-8 It has been suggested that a Campylobacter associated gastritis (CAG) may actually cause dyspeptic complaints.8

The question of whether C pylori is of pathogenetic significance for gastritis and non-ulcer dyspepsia could be answered by using drugs that are active against C pylori.

There are several in vitro studies on the susceptibility of C pylori for different drugs. C pylori appeared to be susceptible for many antibiotics such as ampicillin, erythromycin, gentamycin and ciprofloxacin, while being insensitive to suctalfate and cimetidine in normal pharmacological dosages. In addition C pylori appears to be sensitive to bismuth preparations, such as colloidal bismuth subcitrate (CBS) in low dosages.11-15

We therefore decided to carry out a prospective double blind placebo controlled trial in order to evaluate the effect of CBS on Campylobacter...

Address for correspondence: R J L F Loffeld, Department of Internal Medicine, University Hospital Maastricht, PO Box 1918 6201 BX Maastricht, The Netherlands.

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associated gastritis in patients with non-ulcer dyspepsia.

Methods

Patients

One hundred and forty five consecutive patients with upper abdominal complaints referred to the endoscopy department for upper gastrointestinal endoscopy were studied prospectively for the presence of Campylobacter associated gastritis. Patients with gastric or duodenal ulcers, reflux oesophagitis, active duodenitis, gastrectomy and carcinomas as well as patients using non-steroidal anti-inflammatory drugs or antibiotics were excluded. In view of a possible teratogenic effect and accumulation of the drug pregnant women and patients with renal insufficiency were also excluded from participation. Eighty six patients (59%) showed gastritis histologically with presence of C. pylori proven by histological examination and/or positive culture. Of these 57 (66%) gave informed consent and entered the study.

The 57 patients comprised of 30 men and 27 women, seven were excluded for the following reasons: during revision two patients appeared to have normal gastric histology at entry of the study, five patients were not compliant with therapy, three were taking CBS and two took placebo.

Fifty patients (27 men, 23 women, mean age 48 years, range 18–73) concluded the blind treatment, 34 patients gave informed consent for the open treatment.

All patients were treated blindly with colloidal bismuth subcitrate (CBS. De-Nol) 240 mg bid or placebo during 28 days, subsequently they received an open treatment with CBS 240 mg bid during another 28 days. All preparations were provided by Gist-Brocades Farmaca.

Patients were evaluated before treatment and within 24–72 hours after discontinuation of the blind as well as the open treatment. Evaluation consisted of a standard history using a questionnaire including present complaints, smoking habits, alcohol consumption, medication and family history for upper abdominal complaints.

All patients were subjected to upper gastrointestinal endoscopy after being starved for at least eight hours. Endoscopy was performed, without local anaesthetic, using an Olympus GIF Q gastroscope and biopsies were taken from the gastric antrum for culture (1×) and histological examination (3×), and from the gastric corpus for histological examination (1×).

The questionnaire was repeated and changes of complaints were recorded. Besides overall assessment (unchanged, improved, worsened or disappeared) five dyspeptic symptoms (pain, heartburn, nausea, burping and meteorism) were scored as present, absent, diminished or increased. Examination of the containers returned by the patients indicated compliance with treatment.

The study was approved by the medical ethics committee of the University Hospital of Maastricht.

The χ² test was used for statistical analysis.

Histology

The biopsies were fixed in Bouin’s fixative. Sections were stained with haematoxylin and eosin for histological grading of gastritis according to a modified Whitehead classification. Grade 0: gastric histology within normal limits; grade 1: slight increase of mononuclear cells but within normal limits; grade 2: increase of mononuclear cells, polymorphonuclear cells present; grade 3: increase in mononuclear and polymorphonuclear cells also invading the epithelium.

Biopsies showing features consistent with Whitehead grades 2 and 3 were considered to be showing gastritis, whereas Whitehead grades 0 and 1 were regarded as being within normal histological limits. Change of histology from Whitehead grade 3 to grade 2 and from grade 3 or 2 to grade 1 or 0 was considered as improvement or cure of gastritis respectively.

Sections for the histological detection of Campylobacter like organisms (CLO’s) were stained with a modified Giemsa stain. For semiquantitative grading of presence of CLO the following criteria were used: grade 0: no bacteria detected; grade 1: sporadic bacteria observed; grade 2: many bacteria seen in most microscopic fields at high power magnification (400×); and grade 3: clusters of microorganisms found in the superficial mucus layer in all fields examined.

All biopsies were reviewed before final analysis. The biopsies were studied by two pathologists without prior knowledge of clinical data.

Microbiology

One biopsy was put in sterile saline 0·9% and then transported to the microbiology department for culture. The biopsies were incubated on a blood agar medium of 6% sheep blood under microaerophilic conditions (CO₂ 10%, O₂ 2·5%), during five to seven days at 37°C.

The culture was regarded as positive when the typical colonies of C. pylori were seen. If culture still did not show growth after seven days it was regarded negative.

If culture was positive and the histology failed to show CLO’s, the histological grading for presence of CP was considered to be grade 1.
Results

The blind treatment was concluded by 50 patients, 26 received CBS (13 men, mean age 47 years, range 32–67, and 13 women, mean age 48 years, range 18–70) and 24 placebo (14 men, mean age 38 years, range 22–73 and 10 women, mean age 57 years, range 38–65). Eighteen patients of the CBS group and 17 patients of the placebo group entered the additional open treatment. The others refused further therapy because of sufficient subjective improvement or because of fear of repeated upper gastrointestinal endoscopy.

At entry of the study there was no significant difference in sex, age, subjective complaints, degree of gastritis according to Whitehead or semiquantitative grading of C. pylori presence between the CBS and the placebo group (Tables 1, 2, and 3).

CBS and Gastritis

In Table 1 the correlation between CBS or placebo administration and gastritis score is shown. As can be seen the percentage of patients with grade 3 gastritis was reduced from 88 to 38 after 28 days of CBS, whereas no further reduction was obtained after 56 days. In contrast, after 28 days of placebo administration no effect on the percentage of patients with grade 3 gastritis was observed. After 28 days of CBS therapy, however, a significant reduction of grade 3 gastritis was noted. Figure 1 shows the changes in histology of the individual patients.

Normalisation of gastric histology occurred in nine (35%) patients of the CBS group and in one (4%) patient of the placebo group (p=0.02).

CBS and C. pylori Presence

Table 2 shows the influence of CBS or placebo on the presence of C. pylori after 28 and 56 days of therapy respectively. The percentage of patients with grade 3 presence was reduced from 38 at start of the therapy to 12 after 28 days of CBS and a further reduction was obtained after 56 days of therapy. No such effect was found in patients given placebo treatment. Grade 3 presence was significantly reduced after the open CBS treatment course in these patients. Figure 2 shows the changes of the individual patients.

In one patient of the CBS group endoscopy after CBS revealed a small gastric ulcer located at the angulus, this patient did not show any improvement of gastritis score. After the additional course of CBS it was healed. One patient of the placebo group showed a duodenal ulcer after 28 days of placebo therapy that healed after CBS.

CBS and Symptoms

As shown in Table 4 overall assessment of subjective changes of complaints revealed improvement in half of the patients given CBS, 30% recorded no change, 16% became free of complaints and one patient noted worsening of his complaints as a result of the peptic ulcer. Seventy one per cent of the patients given placebo recorded improvement, whereas none
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Fig. 1 Changes in gastritis score after CBS and placebo treatment. 1st means after CBS and placebo treatment respectively, 2nd means after open treatment with CBS.

Fig. 2 Changes in CLO presence between the CBS group and the placebo group.
became free of complaints. The remainder noted no change. There appeared to be no significant difference in overall assessment between both groups. There was no significant difference between the five symptoms that were recorded separately in both groups. All symptoms showed the same improvement (Table 5). Figure 3, however, shows that the percentual improvement of nausea and meteorism in the CBS group was better.

Discussion

In the literature there are several reports on the effect of bismuth on gastritis and Campylobacter pylori in patients with non-ulcer dyspepsia.26-28 The results of these studies show that there is a resolution of gastritis after suppresson or eradication of C pylori. The majority of these studies, however, failed to provide exact information on inclusion criteria, standardisation of gastritis and C pylori scores.

In addition the best available data on the treatment of Campylobacter associated gastritis, especially with bismuth, have been based on non-controlled trials.29

Bismuth salts have two effects: they are bactericidal for C pylori and they can protect the gastric mucosa against erosive properties of alcohol and aspirin. Bismuth may protect the mucosa from gastric acid with subsequent resolution of gastritis with alteration of the gastric milieu, which is unfavourable for C pylori. Sucralfate has no bactericidal effects on C pylori, and it has no beneficial effect on histologically confirmed gastritis. This suggests that it is the antimicrobial activity of bismuth that is important. C pylori produces a protease which undermines the integrity of the mucus layer. Therefore, because of its bactericidal effect bismuth may have an indirect favourable effect on gastric mucosa.27

McNulty et al reported on a double blind study of bismuthsalicylate.28 77-8% of their patients receiving bismuth were cleared of C pylori after the treatment. This clearance was accompanied with a significant improvement of gastritis score.

The results of our study also show that CBS effectively reduces C pylori colonisation of gastric mucosa and significantly improves signs of gastritis. Complete disappearance of the micro-organism, however, only occurred in a small number of patients, which possibly explains the high percentage of recurrence reported in the literature.29-30 In addition we showed a positive influence of administration of CBS on subjective complaints which, however, largely appeared to be the result of a placebo effect.

Two pertinent aspects of our observations deserve special consideration. First, at day 28 a parallelism in reduction of C pylori presence and gastritis scores was seen in the CBS treated patients, suggestive of a

![Table 4 Subjective changes of complaints](http://gut.bmj.com/content/30/9/1206)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CBS group improvement</th>
<th>CBS group worsening</th>
<th>CBS group no change</th>
<th>CBS group no complaints</th>
<th>Placebo group improvement</th>
<th>Placebo group worsening</th>
<th>Placebo group no change</th>
<th>Placebo group no complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>13 (50%)</td>
<td>1 (4%)</td>
<td>8 (30%)</td>
<td>4 (16%)</td>
<td>17 (71%)</td>
<td>0</td>
<td>7 (29%)</td>
<td>0</td>
</tr>
<tr>
<td>Absent</td>
<td>8 (33%)</td>
<td>14 (58%)</td>
<td>19 (73%)</td>
<td>4 (14%)</td>
<td>3 (13%)</td>
<td>7 (31%)</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Diminished</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

![Table 5 Changes in different complaints after treatment](http://gut.bmj.com/content/30/9/1206)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Present (%)</th>
<th>Absent (%)</th>
<th>Diminished (%)</th>
<th>p=ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>CBS</td>
<td>Placebo</td>
<td>CBS</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>9 (35%)</td>
<td>11 (46%)</td>
<td>8 (30%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>CBS</td>
<td>Placebo</td>
<td>CBS</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>6 (23%)</td>
<td>7 (29%)</td>
<td>19 (73%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>CBS</td>
<td>Placebo</td>
<td>CBS</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>6 (23%)</td>
<td>8 (33%)</td>
<td>11 (42%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>Burping</td>
<td>CBS</td>
<td>Placebo</td>
<td>CBS</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>8 (31%)</td>
<td>7 (29%)</td>
<td>12 (46%)</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>Meteorism</td>
<td>CBS</td>
<td>Placebo</td>
<td>CBS</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>7 (27%)</td>
<td>12 (50%)</td>
<td>15 (58%)</td>
<td>4 (15%)</td>
</tr>
</tbody>
</table>

![Fig. 3 Percentual changes in complaints after treatment in the CBS and the placebo group](http://gut.bmj.com/content/30/9/1206)
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causative role of \textit{C. pylori}. Subsequent administration of CBS, however, only resulted in further clearance of \textit{C. pylori} and no further improvement of gastritis scores was noted. It is conceivable that this discrepancy is the result of a longer period of time necessary for resolution of all signs of inflammation. It would, therefore, be interesting to evaluate gastric biopsies for the presence of gastritis some time after cessation of CBS treatment. On the other hand, the findings can be satisfactorily explained on the basis of the assumption that bacterial clearance and improvement of gastritis basically are two independent processes. In this context it could be hypothesised that Campylobacter associated gastritis is caused by multiple aetiologic agents among which is \textit{C. pylori}. Reduction of the impact of \textit{C. pylori} would then eliminate its contribution in the inflammatory response leaving the influence of inflammatory impetis unaffected. Finally, it may be possible that the remaining gastritis is the result of a small number of \textit{C. pylori} still present after therapy, implying that more effective therapy could cure all signs of gastritis.

In keeping with the findings in the literature we found no significant effect of placebo therapy on gastritis nor on \textit{C. pylori} colonisation. A second point of considerable concern raised by our data is that there appeared to be no difference in improvement of subjective complaints between CBS and placebo treated patients. There are several conflicting studies on the effect of bismuth on complaints in patients with non-ulcer dyspepsia and Campylobacter associated gastritis. Some authors observed significant reduction in several complaints,\textsuperscript{20,22,24,31} whereas others found no difference between \textit{C. pylori} patients treated with bismuth or placebo.\textsuperscript{28} As it is known from the literature that asymptomatic subjects may show signs of gastritis in their biopsies,\textsuperscript{32} we feel that the discrepancy we observed between improvement of \textit{C. pylori} presence and gastritis scores effected by CBS on the one hand, and the lack of a difference of CBS on subjective complaints as compared with controls on the other, is probably caused by a non-existent direct relationship between gastritis and dyspepsia. We conclude that CBS appears to be effective in the elimination of \textit{C. pylori}, diminishes the degree of gastritis but has a positive effect on dyspeptic complaints which is largely the result of a placebo effect. Our data once again question the clinical significance of gastritis in relation to dyspeptic complaints and also cast doubt on the clinical relevance of therapeutic measures aimed at eradication of \textit{C. pylori}.

References


20 Rokkas T, Pursey C, Simmons NA, Filipe MI, Sladen GE. Non-ulcer dyspepsia and colloidal bismuth subcitrate therapy, the role of Campylobacter pyloridis [Abstract 213]. Gastroenterology 1987; 92: Suppl.


