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Clinical trial

Randomised open controlled trial of colloidal bismuth subcitrate tablets and cimetidine in the treatment of duodenal ulcer

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SUMMARY In a study of 28 outpatients with endoscopically proven duodenal ulcers, 14 patients (with a total of 15 ulcers) were treated with bismuth tablets (colloidal bismuth subcitrate, De-Nol, Gist-Brocades NV) and 14 patients (14 ulcers) were treated with cimetidine (Smith, Kline, and French). Clinical and endoscopic assessments were made after four and six weeks' therapy. After four weeks, 10 of the bismuth treated ulcers (67%) and eight of the cimetidine treated ulcers (57%) were completely healed. After six weeks of therapy, complete healing was seen in 86% of both the bismuth treated and the cimetidine treated ulcers. Twenty of the 24 completely healed ulcer patients (10 of each group) cooperated in a three month follow-up study. Pain recurred in three patients of the bismuth group and four of the cimetidine group and they were examined endoscopically. A recurrent ulcer was found in one of the bismuth treated patients and in three of the cimetidine treated patients. These observations indicate that colloidal bismuth subcitrate was at least as effective as cimetidine in the healing of duodenal ulcer.

The discovery of the H_2 histamine receptor blockers has been a major pharmacological break through. However, early work with metiamide was disappointing because of the incidence of side-effects—in particular, bone marrow suppression[1] and parietal cell hypertrophy.[2] Cimetidine has been associated with few side-effects, though reports of gynaecomastia[3] raised serum creatinine and transaminase concentrations,[4,5] increased prolactin levels,[6] mental confusion,[7] and the occurrence of silent perforation of peptic ulcer after abrupt withdrawal of cimetidine,[8] have been published. 'Healing' rates that have been reported after six weeks' cimetidine therapy range from 57 to 93% in the treatment of patients with duodenal ulcers.[9,10] Patients suffering from gastric ulcers seem to respond to a lesser degree to cimetidine therapy; healing rates from 69 to 78% were found by some investigators,[11,12] while others could find no difference between cimetidine and placebo.[13–15] 'Healing' rates of duodenal ulcers after four to six weeks of colloidal bismuth treatment range between 66% and 90%.[16–18] Although direct comparison between separate studies is obviously difficult, the reported rates of healing suggest that, in short-term therapy, cimetidine has no advantage over colloidal bismuth subcitrate. One drawback associated with this liquid bismuth therapy is the taste, which some patients find unpleasant. The aim of this study was to compare the efficacy of colloidal bismuth subcitrate tablets (a new formulation designed to overcome the problems of taste) and cimetidine tablets in the treatment of duodenal ulcer.

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Methods

SELECTION OF PATIENTS

The trial was carried out with 28 patients, 21 men and seven women. The main criteria for inclusion in the trial were the presence of an endoscopically proven duodenal ulcer and the informed consent of the patients to take part in the study. Patients with previous gastric or intestinal surgery, patients with severe renal insufficiency, pregnant women, and patients with debilitating conditions likely to interfere with tissue healing —for example, leukaemia— were excluded from the study. Patients being concurrently treated for duodenal ulcer were also excluded. The series comprised all consecutive patients found at endoscopy to have a duodenal ulcer and to fit the above-mentioned selection criteria. The study

was approved by the Human Research Committee of the University Hospital.

EXPERIMENTAL DESIGN

All patients were treated as outpatients and were randomly assigned to cimetidine or colloidal bismuth subcitrate. Cimetidine was administered in a dose of 200 mg with each meal three times per day and 400 mg at night. Bismuth had to be taken four times a day, one tablet ½ hour before each of the three meals, and two hours after the last meal. Only one antacid formulation (aluminium hydroxide) was prescribed. Vials containing a known number of antacid tablets were given to the patients, who were instructed to take one tablet only when necessary because of severe pain and not to take it within one hour of the cimetidine or bismuth tablet. No dietary restrictions were imposed.

The clinician who took care of the patients and assessed the symptoms and the endoscopist who assessed ulcer healing examined the patient separately and independently of each other.

ENDOSCOPIC ASSESSMENT

The endoscopic examinations were performed in all patients on the first day of treatment and after 28 and 42 days by the same endoscopist using an Olympus GIF-K gastroscope. The endoscopist had no access to the clinical data and did not talk to the patients about treatment given or the results of treatment. At each examination the site of the ulcer was recorded and the diameters were measured using an open biopsy forceps placed in contact with the ulcer. To evaluate the endoscopic appearance of healing after four and after six weeks' therapy the following categories were used: (1) ulcer completely healed—that is, healed without any visible tissue defect; (2) ulcer healed with erosion—that is, the original ulcer was healed but with erosion at site of original ulcer or in close proximity; (3) ulcer diminished in size; (4) no change in ulcer size; (5) enlargement of original ulcer; (6) new ulcer—that is, development of ulcer at another site.

SYMPTOM ASSESSMENT

The clinical assessments were made before treatment and after four and six weeks' therapy. Pain was scored from 1=none to 4=severe pain. The number of cigarettes, cigars, and/or pipes smoked per day was recorded. Alcohol consumption was recorded as daily, seldom, or none, and the mean number of cups of coffee drunk per day was also noted. The presence or absence of constipation, diarrhoea, anorexia, nausea, vomiting, heartburn, waterbrash, and skin rashes were recorded. Systolic and diastolic blood pressure and body weight were noted. Patients were provided with diary notebooks to record the daily intake of antacid tablets, the presence or absence of pain, and the occurrence of pain relief.

LABORATORY TESTS

Haemoglobin, haematocrit, red cell count, white cell count (total and differential), creatinine, urea, calcium, phosphate, bicarbonate, bilirubin, alkaline phosphatase, thymol turbidity, glutamic oxalacetic transaminase, and glutamic pyruvate transaminase determinations were performed at each visit. Blood bismuth levels were determined by atomic absorption spectrophotometry.[18] The sensitivity of the method of bismuth determination was 0·01 μg for 1% absorption, giving a detection limit of 3 μg/l of blood. The coefficient of variation, estimated at a level of 400 μg/l, was 9%.

STATISTICAL ANALYSIS

The data were analysed using either Student's t test the exact Fisher test, or the χ^2 test. The change of bismuth levels was analysed with Wilcoxon's ranked sign test. P values less than 0·05 were considered significant.

FOLLOW-UP STUDIES

At the end of the trial all completely healed patients were asked to cooperate in a follow-up study of three months. Patients were provided with sheets to record daily the presence or absence of pain and they were asked to return for a control endoscopy if ulcer-like pain persisted for more than two days. They returned at monthly intervals for an interview and a clinical examination.

Results

PATIENT PROFILE

Twenty-eight patients were enrolled in the study; 14 patients were treated with colloidal bismuth subcitrate tablets and 14 with cimetidine. Between week four and six, one bismuth treated patient (found to have complete ulcer healing on endoscopy at four weeks) took added ulcer healing agents and was thus ommitted from the sixth week assessment. The mean age of the 14 bismuth treated patients (44·2 years) was not significantly different from that of the cimetidine treated patients (45·3 years). The ratio men/women in the bismuth group (10/4) was not significantly different from that in the cimetidine group (11/3). The mean duration of peptic ulcer disease was 53·1 months in the bismuth group (range 0–138 months), and 77·1 months in the cimetidine group (range 0–192 months). Patients had ulcer symptoms for nine weeks on average in the bismuth group (range 1–44 weeks) and for 13 weeks in the

cimetidine group (range 1–52 weeks). The individual variations were so great that there was no significant difference between the bismuth and cimetidine groups in respect of duration of peptic ulcer disease or of ulcer symptoms.

The size of the ulcer was determined by measuring its 'large' and 'small' diameter. The initial mean large diameter of the ulcer in the bismuth treated group was 9·3 mm (range 4–16 mm) and the initial mean small diameter was 6·7 mm (range 2–14 mm). In the cimetidine treated group the initial mean large diameter was 6·1 mm (range 4–13 mm) and the initial mean small diameter was 5·8 mm (range 3–10 mm). Although the calculated ulcer size of the bismuth group was almost twice that of the cimetidine group (222 mm^2 and 126 mm^2), the difference was not statistically significant.

Table 1 *Endoscopic assessment of ulcer healing after four weeks*

	Bismuth (15 ulcers)*		*Cimetidine (14 ulcers)*	
	(No.)	*(%)*	*(No.)*	*(%)*
Completely healed	10	67	8	57
Healed with erosions	4	26	5	36
Diminished in size	1	7	0	
No change	0		0	
Worse	0		0	
New ulcer	0		1	7

*One patient was found to have two ulcers.

Table 2 *Endoscopic assessment of ulcer healing after six weeks*

	Bismuth (14 ulcers)		*Cimetidine (14 ulcers)*	
	(No.)	*(%)*	*(No.)*	*(%)*
Completely healed	12	86	12	86
Healed with erosions	1	7	2	14
Diminished in size	0		0	
No change	0		0	
Worse	0		0	
New ulcer	1	7	0	

ENDOSCOPIC ASSESSMENT

Fifteen ulcers were diagnosed at initial endoscopy in the 14 patients assigned to the bismuth group. In the cimetidine group 14 ulcers were diagnosed in the 14 patients. The results of the endoscopic assessment after four weeks of treatment are summarised in Table 1. There were no significant differences between colloidal bismuth subcitrate tablets and cimetidine in respect of the ratio of 'completely healed' and 'not completely healed' ulcers.

Table 2 summarises the results of the endoscopic assessment of ulcer healing after six weeks of therapy. The percentage of 'completely healed' ulcers was exactly the same in the two groups and there were no significant differences in respect of the other parameters of healing.

Table 3 *Mean pain scores*

	Bismuth	*Cimetidine*
Before treatment	3·0	2·9
After 4 weeks	1·4	1·3
After 6 weeks	1·4	1·4

Table 4 *Results of three month follow-up after treatment with cimetidine or bismuth**

	Examined clinically	*Symptom free*	*Examined endoscopically*	*With ulcer*	*With erosions*
Cimetidine group	10	7	3	3	1
Bismuth group	10	6	4	1	2

*Numbers represent the number of patients in each category.

SYMPTOM ASSESSMENT

After one week six patients of the bismuth treated group and eight of the cimetidine treated group were free of pain. After two weeks these figures were eight and nine respectively. The mean pain scores in the bismuth and in the cimetidine treated patients before therapy and after four and six weeks' treatment are summarised in Table 3. In both groups the reduction of the scores for pain after four and six weeks was highly significant ($P<0·0001$). No differences were observed between cimetidine and colloidal bismuth subcitrate tablets in the relief of pain after four and six weeks of therapy. The therapy had no effect on the occurrence of constipation, diarrhoea, and anorexia. Both bismuth and cimetidine treated patients showed less nausea after four and six weeks' treatment than before therapy, but bismuth and cimetidine were not significantly different in this respect. After treatment vomiting had completely disappeared in the two groups. Heartburn was significantly improved in the cimetidine group after four and six weeks' treatment. The bismuth treated group showed an improvement which was almost significant at the 5% level after four weeks' treatment but no effect could be demonstrated after six weeks.

EFFECT OF THERAPY ON OTHER MEASUREMENTS

No adverse reactions were observed in respect of blood pressure or the various laboratory tests.

The blood bismuth levels after four weeks (median 5 μg/l), or after six weeks (median 6 μg/l) therapy with colloidal bismuth subcitrate tablets were insignificantly higher than those before treatment.

FOLLOW-UP STUDIES

Twenty of the 24 completely healed ulcer patients co-operated in the three month follow-up study. Ten

patients belonged to the cimetidine treated group and 10 to the bismuth treated group. Epigastric pain recurred in three patients in the cimetidine group and four patients in the bismuth group. Only patients who had symptoms were prepared to undergo another endoscopy. Three patients, previously treated with cimetidine, and one patient, who had been treated with collodial bismuth subcitrate, had an active ulcer. One patient of the cimetidine group and two of the bismuth group had erosive duodenitis, the latter without ulcer.

Discussion

The trial was not double blind. The clinician who took care of the patients could, by talking to the patient, perhaps guess which of the two drugs was being taken and, therefore, his assessment of symptomatic improvement might be biased. The assessment of ulcer healing by the endoscopist, however, could not be biased, because he had no access to the data about treatment or the symptomatic result of treatment and he did not discuss these topics with the patient. Both after four and after six weeks' therapy no differences were observed in the degree of ulcer healing. It may be stressed that an erosion at the site of the original ulcer or in its immediate proximity was taken as an indication of incomplete healing. At the end of six weeks' therapy both bismuth and cimetidine resulted in 86% 'complete' ulcer healing. As the original ulcer size of the bismuth treated group was almost twice that of the cimetidine group, the results indicate that a tablet formulation of colloidal bismuth subcitrate was at least as effective in the healing of the duodenal ulcers as cimetidine in a dose of 1 g per day. In the absence of a placebo control group, the equal results could mean that cimetidine and colloidal bismuth subcitrate were equally ineffective. However, the placebo healing rate in our hospital is less than 45%. Even in the United States the placebo healing rates have not been higher than 60% and have not approached the 86% complete healing observed in both the cimetidine and the bismuth treated groups at six weeks of therapy. The amount of antacids taken in the present study was small, because the patients were allowed to take antacids only if they had severe pain. It is highly unlikely that a 'complete healing' rate of 86% could be due to so small an amount of antacids. If those patients with ulcer healing, but some remaining erosions, are also included, the cure rates are 93% for colloidal bismuth subcitrate and 100% for cimetidine. Clearly such preparations can only be regarded as 'effective'.

The assessment of the symptomatic improvement suggests that the two drugs were equally effective in reducing pain, nausea, and vomiting. Cimetidine was superior to bismuth in the symptomatic improvement of heartburn. Adverse side-effects on blood pressure or on the various laboratory tests did not occur. None of the patients taking the colloidal bismuth subcitrate tablets found the taste to be unpleasant.

Blood bismuth determinations were performed before treatment and after four and six weeks of therapy because of the neurotoxicity that has been seen in some patients on long-term therapy with very high doses of bismuth subnitrate[19 20] or bismuth subgallate.[21 22] In this trial no symptoms of neurotoxicity were observed and blood bismuth levels remained much lower than those associated with bismuth neurotoxicity. It is very unlikely that problems would ever arise with the small quantities of bismuth ingested during the four to six weeks of colloidal bismuth subcitrate therapy (480 mg of bismuth compound, calculated as bismuth oxide, or 430 mg Bi per day) compared with up to 7 g Bi per day taken by patients suffering from neurotoxicity in France, and 750 mg Bi per day often for years in the group of patients treated for colostomy control in Australia who developed neurotoxicity. Moreover, Thomas *et al.*[23] have shown that colloidal bismuth subcitrate is less lipophilic than the subnitrate or subgallate and may thus be less readily absorbed. Blood levels associated with liquid bismuth subcitrate ingestions have never been found to exceed a 50 μg/l level regarded as normal during bismuth therapy by Hillemand *et al.*,[24] let alone approach the blood levels of between 100 μg/litre and 2000 μg/litre[20] seen in patients with bismuth neurotoxicity.

The follow-up studies re-emphasise the high incidence of recurrent ulcer after a course of medical treatment. All but one of the patients who had pain for more than two days were found on endoscopy to have either a recurrent ulcer or erosions in the duodenal bulb. The number of recurrent ulcers in the cimetidine group was larger than in the bismuth group, but this series was too small to draw firm conclusions in this respect. Our studies, however, indicate that colloidal bismuth subcitrate tablets were at least as effective as cimetidine in the healing of duodenal ulcer. Ulcers healed by bismuth were at least as likely to stay healed as ulcers healed by cimetidine.

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