

Bismuth subsalicylate in the treatment of H₂ blocker resistant duodenal ulcers: role of *Helicobacter pylori*

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Abstract

Fifty nine patients with *Helicobacter pylori* positive duodenal ulcers that failed to heal after a six week course of treatment with H₂ blockers were randomly assigned to one of the following three regimens: (i) bismuth subsalicylate, 600 mg three times daily (n=19), (ii) ranitidine, 300 mg at night (n=20), (iii) bismuth subsalicylate plus ranitidine (n=20). Cumulative ulcer healing rates after four and eight weeks respectively were as follows: bismuth subsalicylate 74% (14/19) and 95% (18/19), ranitidine 40% (8/20) and 65% (13/20), bismuth subsalicylate plus ranitidine 80% (16/20) and 95% (19/20). Bismuth subsalicylate treatment was better than ranitidine at both four and at eight weeks (p<0.05). The clearance rates for *H pylori* after four weeks were: bismuth subsalicylate 58%, ranitidine 0%, bismuth subsalicylate plus ranitidine 55%. After stopping bismuth therapy bacterial recrudescence frequently occurred. After bismuth treatment 86% (19/22) of ulcers had healed if *H pylori* had been cleared, whereas only 65% (11/17) had healed if *H pylori* persisted (NS). This study shows that bismuth subsalicylate is more effective in the treatment of resistant duodenal ulcers than standard dose ranitidine. It may be that suppression of *H pylori* by bismuth subsalicylate promotes ulcer healing.

Approximately 85-95% of duodenal ulcers heal within six to eight weeks of treatment with standard doses of H₂ blockers.^{1,2} The reasons for treatment failure remain unclear but inadequate control of acid secretion may be a crucial factor.^{1,3} Recently, the identification of *Helicobacter pylori* and its association with duodenal ulcer disease led to the hypothesis that *H pylori* might be involved in H₂ blocker resistant ulceration.² The successful treatment of H₂ blocker refractory ulcers by colloidal bismuth subcitrate, which is able to eliminate *H pylori*, supports this theory.^{4,5} Unfortunately, the role of *H pylori* was not investigated in these therapeutic trials. Bismuth salts exert bactericidal effects on *H pylori* and have cytoprotective properties as well, thus it is not clear whether the beneficial effect of colloidal bismuth in refractory ulcers is directly related to the elimination of *H pylori*.

This study aimed to investigate the efficacy of bismuth subsalicylate in the treatment of refractory duodenal ulcers and to elucidate the role of *H pylori*.

Methods

PATIENTS AND STUDY DESIGN

Between September 1987 and May 1990 out-

patients with endoscopically proved H₂ blocker resistant duodenal ulcers were recruited to the study. A resistant duodenal ulcer was defined as one that failed to heal after at least six weeks' continuous treatment with cimetidine 800 mg daily or ranitidine 300 mg daily. The largest ulcer diameter was not less than 5 mm. The patients did not have complications of peptic ulcer disease, previous gastric surgery, concomitant treatment with ulcerogenic drugs, anti-coagulants, or antibiotics, or any serious chronic disease. Only patients who had not had antibiotic treatment in the previous six months were included.

At initial endoscopy the ulcer size was assessed and antral biopsy specimens were taken for histological examination and *H pylori* screening. All patients were *H pylori* positive. Detailed information on duration and age of onset of dyspeptic symptoms, previous drug therapy, previous ulcer complications, and social habits were recorded.

After giving informed verbal consent, patients were randomised by a nurse (to guarantee blindness of the investigators) using given regimens stratified for 63 subjects. Randomisation procedure was accomplished by a computer program. Patients were allocated to receive one of the following three treatment regimens: (i) bismuth subsalicylate (Jatrox) 600 mg three times daily (two chewable tablets half an hour before the three meals); (ii) ranitidine (Zantac) 300 mg at night; (iii) bismuth subsalicylate 600 mg three times daily plus ranitidine 300 mg at night. Treatment began within three days of the initial endoscopy and was continued for four weeks. If healing had occurred after four weeks the treatment was stopped; if not the patient continued on the same regimen for another four weeks. If at the end of eight weeks the ulcer had not healed the patient was withdrawn from the trial and ranitidine 900 mg/day was given. No other medications were allowed during the study period.

Compliance was ascertained by counting the number of remaining tablets at the end of each treatment period. Clinical symptoms were assessed by recording the number and severity of pain episodes on a diary card. Endoscopy and *H pylori* screening tests were repeated every four weeks during the course of treatment and four weeks after the end of the trial.

ENDOSCOPY

Endoscopies were performed by PL, SW and JF who were not aware of the clinical data, the bacteriological findings, or the treatment regimen. At each endoscopy five biopsy specimens were taken with sterilised biopsy forceps from antral mucosa 2 cm proximal to the pylorus. Two

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specimens were placed in 2 ml phosphate buffered saline at 4°C for bacteriological examination, two were fixed in 10% formalin for histopathology, and one specimen was used for a rapid urease detecting test (CLO-test, Delta West Ltd, Australia). In addition, smears of biopsy specimens were made for cytological examination using Giemsa staining.

H PYLORI SCREENING

H pylori status was assessed by bacterial culture, a modified Giemsa stain, and the CLO-test as described previously.⁶ Two biopsy specimens were cultured under microaerobic conditions in blood agar base containing 5% horse blood and Skirrow selective supplement for seven days. Cultures were considered positive for *H pylori* if Gram negative, oxidase positive, catalase positive, and urease positive spiral rods were present. The degree of colonisation with *H pylori* was estimated by examination of sections and smears stained with Giemsa and was graded semiquantitatively as follows: 0=no organism; 1=occasional; 2=moderate; 3=large numbers. *H pylori* status was regarded as positive if culture was positive or if the urease test and Giemsa stain were positive.

The term 'clearance' was used if *H pylori* status was negative immediately after stopping treatment. 'Eradication' was used if *H pylori* was absent four weeks after the end of treatment.

HISTOPATHOLOGY

For histological examinations, formalin fixed biopsy samples were embedded in paraffin and sections (4 µm) were stained with haematoxylin and eosin and Giemsa. Each biopsy specimen was assessed for the presence, type, density and localisation of the inflammatory infiltrate. The degree of activity of gastritis was graded (0-3) by estimating the density of polymorphonuclear leukocyte infiltrates as described previously.⁶

STATISTICS

Statistical analysis was carried out by the χ^2 test for the evaluation of the healing rates and by the matched pairs Wilcoxon signed rank test for analysis of *H pylori* and gastritis scores. Differences with p values less than 0.05 were considered significant.

Results

Four of the 63 patients who entered the trial were lost during follow up (bismuth subsalicylate, n=2, ranitidine, n=1, bismuth subsalicylate plus ranitidine, n=1). Fifty nine patients completed the study and their characteristics are shown in Table I. There were no major differences between the three treatment groups. Median age, sex ratio, mean duration of ulcer history, smoking habits, and previous H₂ blocker therapy were comparable (Table I). All patients were *H pylori* positive. No relevant side effects were observed in any treatment group.

Figure 1 summarises the outcome of the patients under the different regimens. After four weeks, ulcer healing had occurred in 74% (14/19) of patients receiving bismuth subsalicylate, in 40% (8/20) of those receiving ranitidine, and in 80% (16/20) of those treated with a combination of both regimens (Table II). In patients with incomplete ulcer healing the same therapeutic regimen was continued for another four weeks. After eight weeks' treatment the cumulative healing percentages were 95% on bismuth subsalicylate, 65% on ranitidine, and 95% on bismuth subsalicylate plus ranitidine. The healing rate on bismuth subsalicylate alone or in combination with ranitidine was significantly higher compared with that on ranitidine, both at four and at eight weeks (p<0.05). There was, however, no significant difference between bismuth subsalicylate as a single agent and in combination with ranitidine. After eight weeks there was no ulcer relapse in patients whose ulcers had healed during a four week course of bismuth subsalicylate while two ulcers relapsed in the ranitidine group.

After four weeks *H pylori* was cleared in 58% of patients receiving bismuth subsalicylate and in 55% of those treated with bismuth subsalicylate plus ranitidine, while none of the patients in the ranitidine group was *H pylori* negative (Table II). At eight weeks only a small group of patients was still negative for *H pylori* (bismuth subsalicylate 21%, bismuth subsalicylate plus ranitidine 20%).

The degree of mucosal infestation with *H pylori* was similar in all treatment groups at trial entry (Fig 2). At four weeks a noticeable reduction in *H pylori* scores was observed in groups treated with bismuth subsalicylate, either alone or in combination with ranitidine. At eight weeks the density of colonisation with *H pylori* increased again in the bismuth groups because treatment had been stopped in the majority of patients whose ulcers had healed after four weeks. In a subgroup of patients who received bismuth subsalicylate for eight weeks *H pylori* scores resembled those at four weeks (data not shown). Ranitidine monotherapy had no significant effect on *H pylori* scores at any time.

TABLE I Patient characteristics and treatment schedules

	BSS (3×600 mg)	Ranitidine (300 mg)	BSS (3×600 mg) plus ranitidine (300 mg)
Patients (n)	19	20	20
Sex (male)	15	13	16
Median age (yrs)	46	47	43
Duration of ulcer history (median (yrs))	9	7	8
Smokers (n)	14	13	11
Pain free (n)	4	6	6
<i>H pylori</i> positive (n)	19	20	20
Pretreatment (6 wks):			
Cimetidine 800 mg/day (n)	14	12	16
Ranitidine 300 mg/day (n)	5	8	4

BBS=bismuth subsalicylate.

TABLE II Ulcer healing rates and Helicobacter pylori status after four and eight weeks' treatment

Treatment	Ulcer healed		<i>H pylori</i> negative	
	4 Weeks	8 Weeks	4 Weeks	8 Weeks
BSS	14/19 (74%)*	18/19 (95%)*	11/19 (58%)	4/19 (21%)
Ranitidine	8/20 (40%)	13/20 (65%)	0/20 (0%)	0/20 (0%)
BSS+ranitidine	16/20 (80%)*	19/20 (95%)*	11/20 (55%)	4/20 (20%)

*p<0.05; BSS v ranitidine and BSS plus ranitidine v ranitidine. BSS=bismuth subsalicylate.

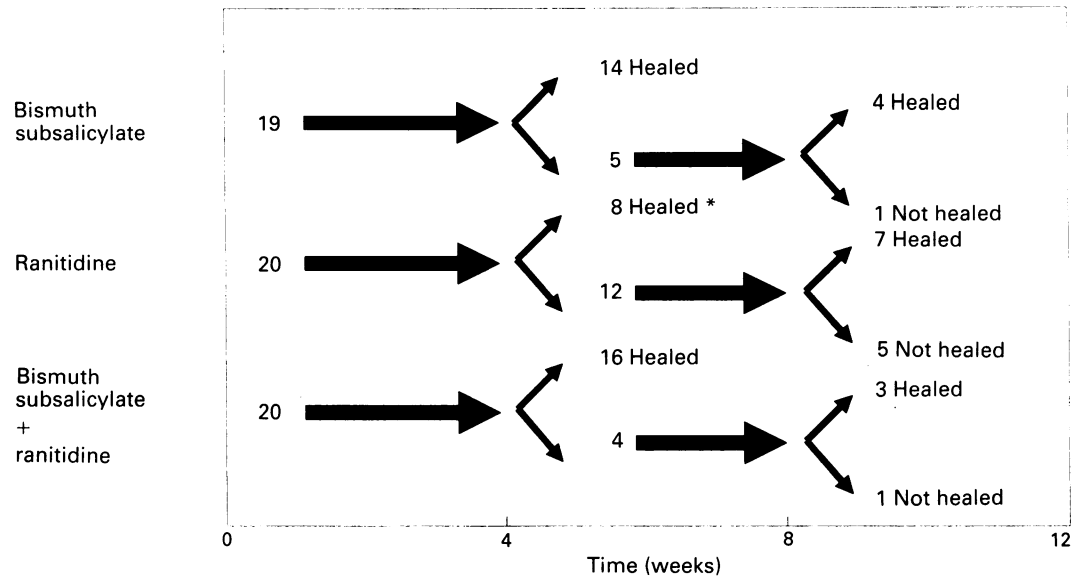


Figure 1: Healing of H₂ blocker resistant duodenal ulcers with bismuth subsalicylate, ranitidine, or both, at four and at eight weeks. *Two relapsed at eight weeks.

In the biopsy specimens of the antrum taken before entry active chronic gastritis was found to a similar extent in all study groups (Fig 3). Gastritis scores fell after four weeks of bismuth subsalicylate and were still somewhat lower at eight weeks in these patients when compared with basal values. In parallel to the *H pylori* scores, ranitidine monotherapy failed to improve gastric inflammation at any time.

Table III shows ulcer healing in relation to clearance of *H pylori* in patients treated with bismuth subsalicylate alone or in combination with ranitidine. Ulcer healing was higher after clearing of *H pylori* in comparison with the permanently infected patients, but this difference did not reach statistical significance (healing rate 86% v 65%; odds ratio 3.15; NS). Some 65% (11/17) of ulcers healed during a four week course of bismuth (alone or combined with ranitidine) despite persistence of *H pylori* in gastric mucosa, even though there had been a reduction in the overall bacterial load.

In order to study the efficacy of bismuth

subsalicylate in eradicating *H pylori*, patients were reinvestigated four weeks after stopping bismuth treatment. Thirty patients received bismuth subsalicylate for four weeks, and of these three were still *H pylori* negative four weeks after completing treatment, resulting in an eradication rate of 10%. Nine patients were treated with bismuth subsalicylate for eight weeks, only one patient (11%) eradicated *H pylori* in this subgroup.

At trial entry epigastric pain was recorded in 14/19, 16/20, and 14/20 respectively in treatment groups (i), (ii), and (iii). Most patients became asymptomatic after two weeks and there was no difference in the proportion of patients with residual symptoms in the three treatment groups.

Discussion

There is no general agreement on the definition of H₂ blocker resistant duodenal ulcers.² Since most ulcers heal after six weeks' treatment with

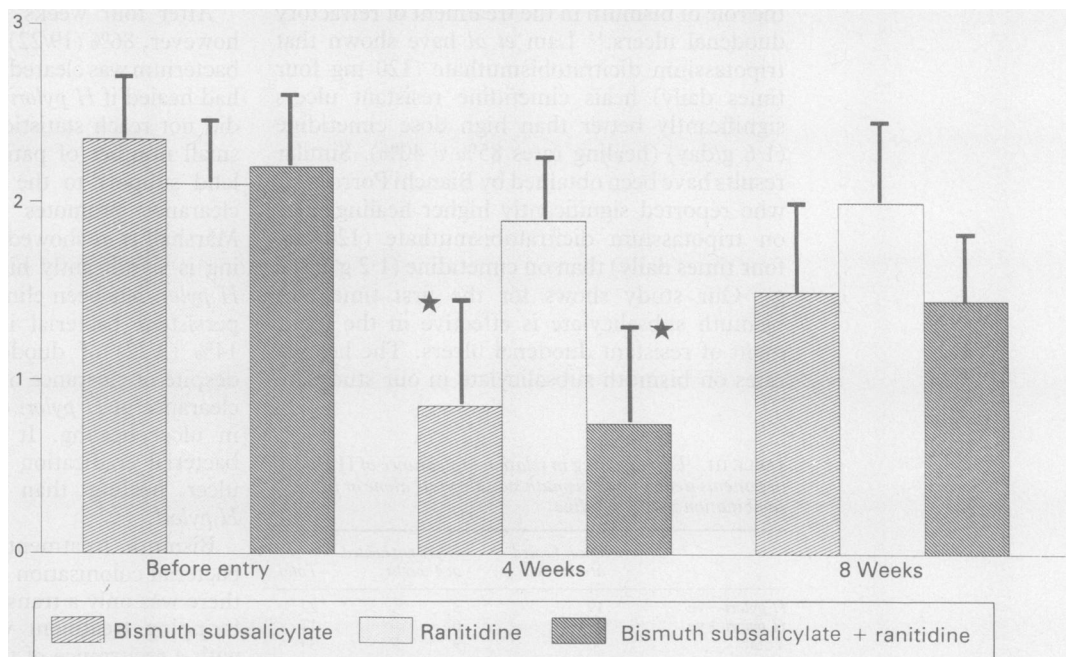
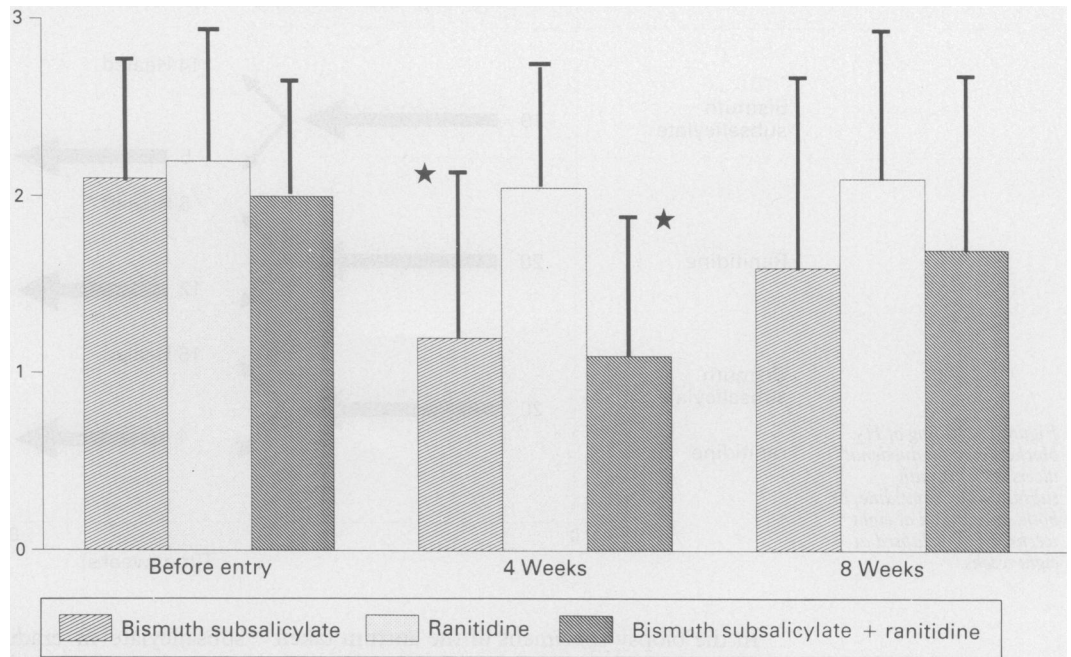


Figure 2: Mean (SD) of H pylori colonisation in antral biopsy specimens under different therapies before treatment and at four and eight weeks. A significant decrease in H pylori colonisation in comparison with the preentry level is indicated by an asterisk.

Figure 3: Mean (SD) scores of gastritis in antral biopsy specimens under different therapies before treatment and at four and eight weeks. A significant decrease in the gastritis score in comparison with the pre-entry level is indicated by an asterisk.



a standard dose of an H₂ blocker, this time criterion was chosen in the present study for the definition of a resistant ulcer.⁷ In our series a further four week course of treatment with ranitidine 300 mg was able to heal 40% of the resistant duodenal ulcers, and 65% were healed after eight weeks. Therefore, only a small group of patients is truly resistant to H₂ blockers, while most represent slow ulcer healing.

Our controlled trial shows that bismuth subsalicylate is superior to standard dose ranitidine in the treatment of resistant ulcers. Both at four and at eight weeks, the healing rate was significantly higher with bismuth subsalicylate than with ranitidine treatment. The combination of bismuth subsalicylate and ranitidine resulted in healing rates similar to those with bismuth subsalicylate alone.

While the efficacy of colloidal bismuth subcitrate in the treatment of duodenal ulcers is well established,⁸⁻¹⁰ only two reports have addressed the role of bismuth in the treatment of refractory duodenal ulcers.^{4,5} Lam *et al* have shown that tripotassium dicitratobismuthate (120 mg four times daily) heals cimetidine resistant ulcers significantly better than high dose cimetidine (1.6 g/day) (healing rates 85% *v* 40%). Similar results have been obtained by Bianchi Porro *et al*, who reported significantly higher healing rates on tripotassium dicitratobismuthate (120 mg four times daily) than on cimetidine (1.2 g and 2 g). Our study shows for the first time that bismuth subsalicylate is effective in the treatment of resistant duodenal ulcers. The healing rates on bismuth subsalicylate in our study are

comparable with those achieved with tripotassium dicitratobismuthate in the trials of Lam *et al* and Bianchi Porro *et al*. Thus, the efficacy of bismuth salts in ulcer healing seems to be related solely to the bismuth component while the anion may be of minor importance.

Bismuth salts are site protective agents which have various cytoprotective properties.¹¹⁻¹⁴ Additionally, they have recently been shown to exert bactericidal effects on *H. pylori*.^{6, 15-17} The present study is the first which attempts to elucidate the role of *H. pylori* in the healing of resistant duodenal ulcers. None of the patients treated with ranitidine cleared *H. pylori*, nor did they show a decrease in the degree of bacterial infestation. Some 65% (11/17) of the duodenal ulcers healed with bismuth subsalicylate despite persistence of *H. pylori*, although at a decreased number. Thus, bacterial elimination is not a prerequisite for healing of resistant duodenal ulcers.

After four weeks' treatment with bismuth, however, 86% (19/22) of ulcers had healed if the bacterium was cleared, whereas only 65% (11/17) had healed if *H. pylori* persisted. This difference did not reach statistical significance due to the small number of patients but the finding may lend support to the hypothesis that bacterial clearance promotes ulcer healing. Recently, Marshall *et al* showed that duodenal ulcer healing is significantly higher in patients in whom *H. pylori* has been eliminated than in those with persistent bacterial infection.¹⁶ In our study, 14% (3/22) of duodenal ulcers did not heal despite of clearance of *H. pylori*, suggesting that clearance of *H. pylori* does not necessarily result in ulcer healing. It could be, however, that bacterial eradication is a stronger promoter of ulcer healing than temporary clearance of *H. pylori*.

Bismuth treatment reduced the density of bacterial colonisation of the gastric mucosa, but there was only a transient clearance of *H. pylori*. Stopping treatment was frequently associated with a recurrence of the organism in the gastric

TABLE III Ulcer healing in relation to clearance of *H. pylori* in patients treated with bismuth subsalicylate alone or in combination with ranitidine

	Ulcer healed at 4 weeks	Ulcer not healed at 4 weeks	Total
<i>H. pylori</i> -ve	19	3	22
<i>H. pylori</i> +ve	11	6	17
Total	30	9	39

mucosa showing that eradication of *H pylori* is a rare event during bismuth treatment. In agreement with previous studies,^{17,18} we found a close relation between the grade of chronic gastritis and the degree of infestation of gastric mucosa with *H pylori*. A reduction in the *H pylori* score was associated with an improvement in gastric inflammation. Therefore, the difference in ulcer healing rates in patients treated with bismuth *v* those treated with ranitidine may be partly a result of an improvement of histology.

The role of *H pylori* in acute ulcer healing seems to be of less importance than its role in the recurrence of duodenal ulcers. A growing body of evidence has accumulated indicating that eradication of *H pylori* is associated with a significant reduction in ulcer relapses and may even cure duodenal ulcer disease.^{15,16,19}

The causes of H₂ blocker ineffectiveness in acute ulcer healing have not been fully clarified. Inadequate acid suppression has been frequently observed in H₂ antagonist non-responders.²⁰⁻²³ In addition, almost all H₂ blocker resistant duodenal ulcers can be healed by the potent proton pump inhibitor omeprazole.^{24,25} Therefore, inadequate control of acid secretion by H₂ blockers seems to be the most important factor in treatment failures.

In conclusion, our study shows that bismuth subsalicylate is effective in the treatment of H₂ blocker resistant duodenal ulcers. In addition, bismuth subsalicylate is superior to a prolonged administration of standard dose H₂ antagonists. The beneficial effects of bismuth subsalicylate in the treatment of resistant ulcers may result from suppression of *H pylori* and the associated improvement of gastritis in addition to its well known cytoprotective properties

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- 1 Wormsley KG. Duodenal ulcers which do not heal rapidly. *BMJ* 1984; 289: 1095.
- 2 Domschke W, Lam SK, Pounder RE, Andersen D. H₂-blocker-resistant duodenal ulceration. *Gastroenterol International* 1989; 2: 85-91.
- 3 Gledhill T, Buck M, Hunt RH. The effect of no treatment, cimetidine 1 g/d, cimetidine 2 g/d and cimetidine combined with atropine on nocturnal gastric secretion in cimetidine non-responders. *Gut* 1984; 25: 1211-6.
- 4 Lam SK, Lee NW, Koo J, Hui WM, Fok KH, Ng M. Randomised crossover trial of tripotassium dicitrato bismuthate versus high dose cimetidine for duodenal ulcers resistant to standard dose cimetidine. *Gut* 1984; 25: 703-6.
- 5 Bianchi Porro G, Parente F, Lazzaroni M. Tripotassium dicitrato bismuthate (TDB) versus two different dosages of cimetidine in the treatment of resistant duodenal ulcers. *Gut* 1987; 28: 907-11.
- 6 Wagner S, Freise J, Bär W, Fritsch S, Schmidt FW. Epidemiologie und Therapie der *Campylobacter-pylori*-Infektion. *Dtsch Med Wochenschr* 1989; 114: 407-13.
- 7 Delchier JC, Isal JP, Eriksson S, Soule JC. Double blind multicentre comparison of omeprazole 20 mg once daily versus ranitidine 150 mg twice daily in the treatment of cimetidine or ranitidine resistant duodenal ulcers. *Gut* 1989; 30: 1173-8.
- 8 Lee FI, Samloff IM, Hardman M. Comparison of tripotassium dicitratobismuthate tablets with ranitidine in healing and relapse of duodenal ulcers. *Lancet* 1985; i: 1299-302.
- 9 Hamilton I, O'Connor HJ, Wood NC, Bradbury I, Axon ATR. Healing and recurrence of duodenal ulcer after treatment with tripotassium dicitrato bismuthate (TDB) tablets or cimetidine. *Gut* 1986; 27: 106-10.
- 10 Tytgat GNJ. Colloidal bismuth subcitrate in peptic ulcer - A review. *Digestion* 1987; 37 (suppl 2): 31-41.
- 11 Konturek SJ, Radecki T, Piastucki I, Drozdowicz D. Advances in the understanding of the mechanism of cytoprotective action by colloidal bismuth subcitrate. *Scand J Gastroenterol* 1986; 21 (suppl 122): 6-10.
- 12 Wagstaff AJ, Benfield P, Monk JP. Colloidal bismuth subcitrate. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in peptic ulcer diseases. *Drug* 1988; 36: 132-57.
- 13 Hall DWR. Review of the modes of action of colloidal bismuth subcitrate. *Scand J Gastroenterol* 1989; 24 (suppl 157): 3-6.
- 14 Ericsson CD, Tannenbaum C, Charles TT. Antisecretory and antiinflammatory properties of bismuth subsalicylate. *Rev Infect Dis* 1990; 12 (suppl 1): S11-5.
- 15 Coghlan JG, Humphries H, Dooley C, Keane C, Gilligan D, McKenna D, et al. *Campylobacter pylori* and recurrence of duodenal ulcers - a 12-month follow-up study. *Lancet* 1987; ii: 1109-11.
- 16 Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow ED, Blackbourn SJ, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet* 1988; ii: 1437-42.
- 17 Rauws EAJ, Langenberg W, Houthoff H, Zanen HC, Tytgat GNJ. *Campylobacter pyloridis*-associated chronic active antral gastritis. *Gastroenterology* 1988; 94: 33-40.
- 18 Stolte M, Eidt S, Ritter M, Bethke B. *Campylobacter pylori* und gastritis - association oder induktion. *Pathologe* 1989; 10: 21-6.
- 19 Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. *Lancet* 1990; i: 1233-5.
- 20 Savarino V, Mela GS, Scalabrini P, Celle G. H₂-receptor antagonist non-responders. *Lancet* 1987; ii: 1281.
- 21 Wagner S, Freise J, Schmidt FW. H₂-receptor antagonist non-responders. *Lancet* 1988; i: 128.
- 22 Johnston DA, Wormsley KG. The effects of fasting on 24-h gastric secretion of patients with duodenal ulcers resistant to ranitidine. *Aliment Pharmacol Therap* 1989; 3: 471-9.
- 23 Collen MJ, Stanczak VJ, Ciarleglio CA. Refractory duodenal ulcers (nonhealing duodenal ulcers with standard doses of antisecretory medication). *Dig Dis Sci* 1989; 34: 233-7.
- 24 Tytgat GNJ, Lamers CBHW, Hameetman W, Jansen JMBJ, Wilson JA. Omeprazole in peptic ulcers resistant to histamine H₂-receptor antagonists. *Aliment Pharmacol Therap* 1987; 1: 31-8.
- 25 Brunner G, Creutzfeldt W, Harke U, Lamberts R. Therapy with omeprazole in patients with peptic ulcerations resistant to extended high-dose ranitidine treatment. *Digestion* 1988; 39: 80-90.