

Amoxicillin plus omeprazole *versus* triple therapy for eradication of *Helicobacter pylori* in duodenal ulcer disease: a prospective, randomized, and controlled study

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Abstract

Treatment with amoxicillin and omeprazole resulted in encouraging *Helicobacter pylori* eradication rates in pilot studies that included medium term follow up. These results were evaluated in a prospective, randomised and controlled study. Forty patients with active duodenal ulcer disease and *H pylori* colonisation of the gastric mucosa were randomly assigned to receive either omeprazole (20 mg twice daily) and amoxicillin suspension (500 mg four times daily) for two weeks (group I) or bismuth subsalicylate (600 mg three times daily), metronidazole (400 mg three times daily), tetracycline (500 mg three times daily), and ranitidine (300 mg in the evening) for two weeks (group II). Study medication was followed in both groups by a four week treatment course with 300 mg ranitidine up to the final examination. One patient from each group was lost to follow up. *H pylori* was eradicated in 78.9% of group I and 84.2% of group II ($p=1.00$). All ulcers in patients on omeprazole plus amoxicillin healed but in the triple treatment group four patients had residual peptic lesions after six weeks (ulcer healing rate: 78.9%, $p=0.11$). Complete pain relief occurred after a median duration of 1 day in group I and of 6 days in group II ($p=0.03$). There were no major complications in either group but minor side effects were more frequently recorded in patients on triple therapy (63.2% *v* 15.8%, $p<0.01$). In conclusion, two weeks of treatment with omeprazole plus amoxicillin is as good as triple therapy plus ranitidine in eradicating *H pylori* but seems better with regard to safety, pain relief, and ulcer healing. Thus, amoxicillin plus omeprazole should be recommended as the treatment of choice in eradicating *H pylori* in patients with duodenal ulcer disease.

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The important role of *Helicobacter pylori* in idiopathic duodenal ulcer disease has been widely acknowledged since the clear demonstration that ulcer relapse or remission is strongly associated with *H pylori* colonisation or absence from the gastric mucosa.¹⁻⁵ *H pylori* therapy is recommended in patients with relapsing duodenal ulcer disease,⁶ but a simple and safe treatment schedule is not yet available. Demanding oral triple therapy eradicates *H pylori* in up to 96% of patients treated^{7,8} but does have considerable side effects.^{9,10} Because of this there has been

scientific and practical interest in the facts that a monoantibiotic regimen comprising omeprazole and amoxicillin has been highly successful in eradicating *H pylori* in some pilot studies¹¹ and has shown good results with regard to *H pylori* reinfection and the clinical course of peptic ulcer disease in the first year after treatment.¹³

These encouraging results in pilot studies required confirmation in prospective and randomised trials. We conducted such a study in patients with active duodenal ulcer disease. The control group was treated with an oral triple therapy regimen which had previously been evaluated in a pilot study.¹⁰

Methods

Forty patients who qualified for admission to the study (Tables I and II) were randomly assigned to receive either omeprazole (20 mg twice daily) (Antra, Astra Chemicals, Wedel/Holstein, Germany) before meals and amoxicillin suspension (500 mg four times daily) (Amoxypen suspension, Grünenthal, Stolberg, Germany) before meals and at bedtime for two weeks (group I) or bismuth subsalicylate (600 mg three times daily) (Jatrox, Röhm Pharma, Weiterstadt, Germany) before meals, metronidazole (400 mg three times daily) (Clont 400, Bayer, Leverkusen, Germany) and tetracycline (500 mg three times daily) (Hostacyclin 500, Hoechst, Frankfurt, Germany) after meals, and ranitidine (300 mg at night) for two weeks (group II). After stopping the study medication all patients in both groups continued treatment with 300 mg ranitidine at bedtime for four weeks up to the final follow up examination.

Before starting treatment patients were talked to and were given an information sheet on the basic concepts of the pathophysiology of *H pylori* infection. They were then asked to participate after a full explanation of the aims and methods of the study, and all gave informed consent. During treatment, patients were asked to consult their study physician if they had side effects. In addition, complaints and side effects were recorded in a diary. Patient compliance was checked with a diary and by counting the number of returned tablets or by calculating the quantity of amoxicillin suspension used, respectively.

Before treatment and after six weeks, patients were investigated clinically, including a symptom score (grade 0: none, grade 1: mild, grade 2: moderate, grade 3: severe complaints due to peptic ulcer disease), and endoscopically. Four

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biopsy specimens of the antrum and four of the gastric body were taken and were analysed by urease test, microscopy of a methylenblue stained mucosal smear, specific culture, and histology after modified Giemsa staining as described elsewhere.^{12,13} Both the microbiologist and the pathologist were blinded to the treatment by coding the samples with random numbers. In addition, all patients were assessed for *H pylori* infection by the ¹³C-urea breath test at the final examination (Prof F E Bauer, University of Göttingen, Germany¹⁴). Eradication was defined as no evidence of *H pylori* infection (by urease test, microscopy, culture, histology, urea breath test) four weeks after stopping the study medication.

The demographic and clinical characteristics were compared statistically by the Wilcoxon rank sum test (age, ulcer history, pain score) or Fisher's exact test (gender, smoker, alcohol use) and the results of treatment by Fischer's exact test or the log-rank test (pain relief). All statistical analyses were two tailed. Differences were considered significant at a 5% probability level.

Results

Forty patients entered the study. The two groups of patients assigned to receive either amoxicillin/omeprazole (group I) or triple therapy plus ranitidine (group II) had similar

TABLE I Patient selection

Inclusion criteria:	
Active duodenal ulcer disease	
<i>H pylori</i> status positive	
Age 18–80 y	
Informed consent	
Exclusion criteria:	
Additional gastric ulcer	
Treatment with omeprazole, bismuth compounds, and antibiotics during the 4 weeks before endoscopy	
History of ulcer surgery including vagotomy (except oversewing of ulcer perforation)	
Pregnancy or lactation	
Renal insufficiency (creatinine >2.0 mg/100 ml; 180 µmol/l)	
Congestive heart failure	
Severe liver disease	
Disorder of clotting	
Known penicillin hypersensitivity	
Lack of compliance	

TABLE II Demographic and clinical characteristics of patients

	Amox/ome (n=20)	Triple therapy* (n=20)	p
Median age (range) (y)	54.5 (24–76)	51.5 (22–75)	0.43
Men/women (n)	14/6	14/6	1.00
Outpatient/hospitalised (n)	13/7	13/7	
Ulcer history, median (range) (y)	10.5 (2–40)	10.0 (0–40)	0.32
First ulcer (n)	0	1	
Median number of ulcers in the last year (range) (n)	2 (0–3)	2 (0–3)	
Complicated ulcer disease:			
Actual bleeding (n)	4	2	
History of bleeding (n)	5	5	
History of perforation (n)	0	2	
Treatment with H ₂ -blockers (n)	12	11	
Aspirin or NSAID use (n)	0	1	
Smoker (n)	9	8	1.00
Alcohol use (n)	13	11	0.75
Median score of epigastric pain	2.5 (0–3)	3 (0–3)	0.33
Ulcer size (mm)	5–30	5–12	
No of ulcers (1/2/3) (n)	20/0/0	16/2/2	

Amox/ome: amoxicillin plus omeprazole.
*Plus ranitidine.

TABLE III Overview of the treatment results

	Amox/ome (n=19)	Triple therapy* (n=19)	p
<i>H pylori</i> eradication (n (%))	15/19 (78.9)	16/19 (84.2)	1.00
Complete ulcer healing (n (%))	19/19 (100)	15/19 (78.9)	0.11
Median duration for pain relief (d)	1	6	0.03
Patients experiencing side effects (n (%))	3 (15.8)	12 (63.2)	0.01

Amox/ome=amoxicillin plus omeprazole.
*Plus ranitidine.

demographic and clinical characteristics (Table II). One patient in each group was lost to follow up. Compliance was good (>95% consumption of the delivered study medication) in all group I patients and in 18 of 19 patients in group II. One group II patient refused his morning medication (bismuth subsalicylate, metronidazole, tetracycline) in the second week because of disturbing fatigue.

Before treatment, *H pylori* colonisation of the gastric mucosa had been detected by urease test and histology in all patients (microscopically after methylenblue staining in 37, and culture in 31 patients).

Epigastric pain was the main clinical symptom of duodenal ulcer disease: this was experienced by all patients before entering the study. Complete pain relief occurred after a median time of 1 day (25% quantile: 0.0–75% quantile: 3.0) in the amoxicillin/omeprazole group and of 6 days (25% quantile: 5.0–75% quantile: 10.0) in the triple therapy group (p=0.03). After six weeks, complete ulcer healing was observed endoscopically in all group I patients and in 15 of 19 patients (78.9%) in group II (p=0.11). We detected residual peptic lesions in the duodenal bulb of four group II patients at the final follow up examination. These were associated with successful *H pylori* eradication in three cases and with treatment failure in one patient. The overall proportion of *H pylori* eradication was 78.9% after combined amoxicillin/omeprazole treatment and 84.2% after triple therapy plus ranitidine (p=1.00).

Before treatment, histology showed that all patients had chronic active gastritis, predominantly in the antral region. Successful *H pylori* eradication resulted in improvement of moderate or severe gastritis in 26 of 31 patients, complete healing of moderate gastritis in one patient, unchanged histology in four patients with mild to moderate lymphocytic infiltration, and total disappearance of polymorphonuclear leukocytes in all but one patient (Figure A, B, D, and E). Treatment failure was accompanied by a slight improvement of gastritis in one patient, by similar histology before and after treatment in four cases, and by worsening gastric mucosal inflammation in two patients (Figure C). In these patients, gastritis activity was improved in three, unchanged in three, and worse in one (Figure F).

There were no major side effects that interrupted treatment in either group. Three patients from the amoxicillin/omeprazole group complained of side effects (15.8%; mouth burning: n=2, pruritus: n=1), whereas undesired effects were reported in 12 of 19 patients in the triple

therapy group (63.2%; diarrhoea: n=4, sleep disturbances: n=2, dizziness: n=2, paresthesias of the legs: n=2, anal pruritus: n=2, mouth burning: n=1, nausea: n=1, fatigue: n=1). All side effects disappeared spontaneously after stopping the study medication. The proportions of minor side effects experienced were significantly different in the two treatment groups ($p < 0.01$).

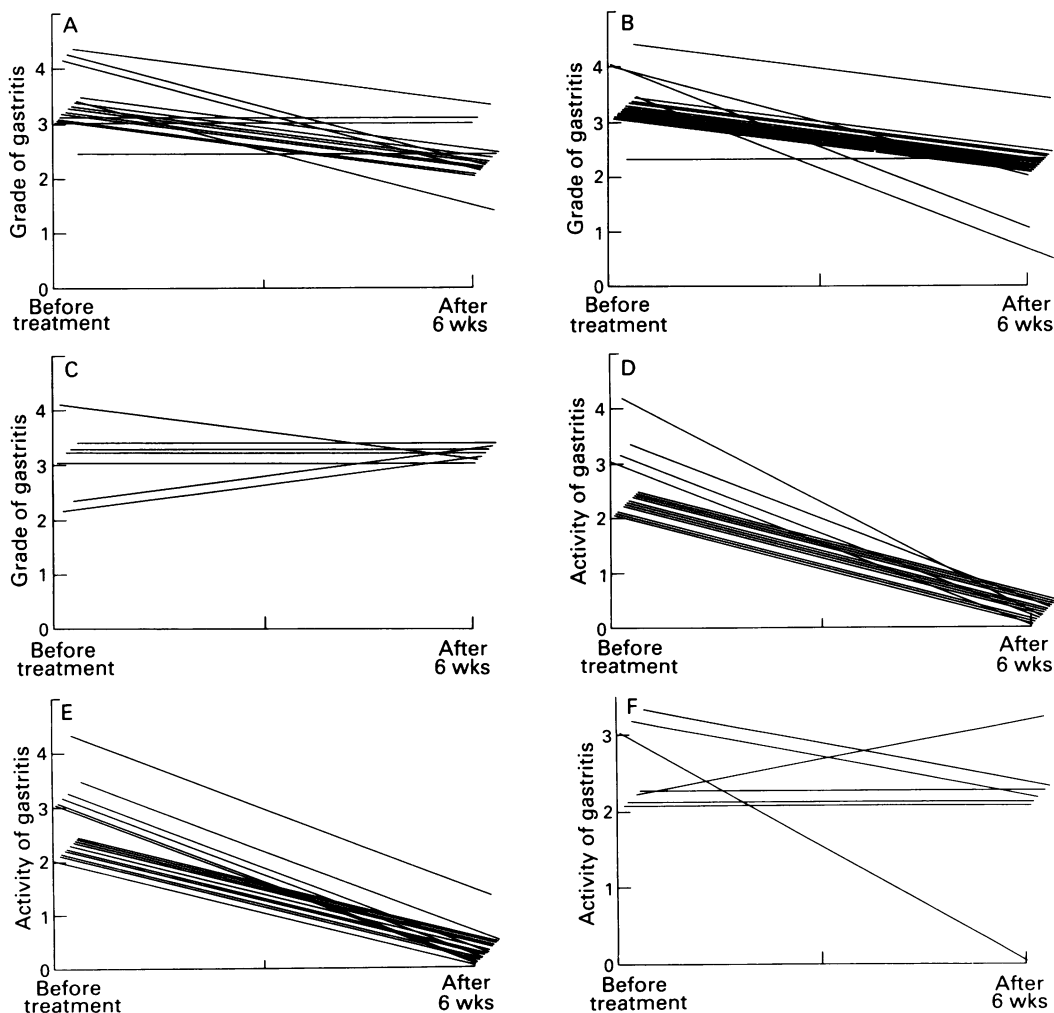
Discussion

Several studies have shown that the eradication of *H. pylori* is associated with a considerable reduction in the rate of recurrence of duodenal and gastric ulcers, but how and why this occurs is still a matter of debate.¹⁵ Because bismuth and antibiotic monotherapy fail to eradicate *H. pylori* in an appreciable proportion of patients,¹⁶ triple therapy (for example bismuth, metronidazole, and tetracycline or amoxicillin) has been tried and is now the treatment of choice.^{6,16} Patients treated with triple therapy, however, complain of considerable side effects which endangers compliance in routine clinical practice. In several pilot studies, we obtained *H. pylori* eradication with a low complication rate in approximately 60–80% of patients treated with an omeprazole modified monoantibiotic therapy with amoxicillin.¹¹ Bacterial eradication resulted in a dramatic change in the natural history of duodenal and gastric ulcer disease in the first year

after treatment.³ These encouraging results were confirmed by Bayerdörffer *et al.*,¹ but other authors reported a lack of efficacy of the combined amoxicillin/omeprazole treatment, probably because of different dosage regimens, the kind of amoxicillin preparation used, or omeprazole pretreatment.^{1,11}

There is still no satisfactory explanation for the much greater efficacy of a combined omeprazole/amoxicillin treatment regimen. Omeprazole alone acts bacteriostatically on *H. pylori* in vitro, with MIC values in the range of bismuth salts,¹⁷ but there are no data on its in vivo mechanism of action. Omeprazole monotherapy merely suppressed bacterial colonisation, especially in the antral region, and eradicated *H. pylori* in individual cases only.¹⁸ It seems more likely that the decisive factor is the improvement in the antibacterial activity of amoxicillin after profound inhibition of acid secretion, because the MIC values of amoxicillin against *H. pylori* are appreciably lower at neutral pH, for example, than at a pH of 5.5.¹⁹ In addition, therapeutically induced anacidity may result in bacterial overgrowth of the stomach, with consecutive displacement of *H. pylori*.^{20,21} The latter hypothesis is supported by the observation that *H. pylori* colonisation is rarely found in patients with anacidity caused by type A gastritis.²²

The promising possibility of omeprazole enhanced antibiotic treatment for *H. pylori* associated diseases cannot be assumed uncondi-



Changes of grade and activity of antral gastritis (1: minimal, 2: mild, 3: moderate, 4: severe) associated with *Helicobacter pylori* eradication induced by amoxicillin/omeprazole treatment (A, D) or oral triple therapy plus ranitidine (B, E). Grade and activity of antral gastritis associated with treatment failure (both groups, C and F).

tionally for antimicrobial compounds other than amoxicillin. In small scale pilot studies omeprazole plus ciprofloxacin or cefixime failed to eradicate *H pylori* in the vast majority of patients.¹¹ In a recently published pilot study, however, an *H pylori* eradication rate of 80% was achieved after two weeks' treatment with omeprazole (40 mg) and the new macrolide antibiotic clarithromycin (500 mg three times daily).²³

In this study, the new treatment strategy of 'anacidity enhanced antibiotic treatment' was compared for the first time with a previously evaluated triple therapy regimen (*H pylori* eradication rate: 92%).¹⁰ The results suggest that these treatment regimens are equally effective in producing *H pylori* eradication, but amoxicillin/omeprazole is better with regard to side effects, pain relief, and probably ulcer healing. There was indeed a trend towards higher eradication rates in the triple therapy group (84.2 v 78.9%), but this lacked statistical significance because of the rather small sample size. A study with the power to show clearly that a 5% yield difference was truly present or absent would have required a prohibitively high number of 2336 study subjects (power 80%). Giving the drugs four times daily in the triple therapy group might have further improved the treatment results. In our experience, however, the three times daily dosing gives eradication rates of approximately 90%, well in accordance with published figures on four times daily dosing. The potential advantage of more frequent dosing would have been at most a rather small one therefore and would not have changed the main conclusions of this study. In Germany, the two treatment schedules evaluated in this study are equally expensive. It therefore seems justified to recommend amoxicillin/omeprazole as the treatment of choice to eradicate *H pylori* in *H pylori* related gastroduodenal diseases. Triple therapy might be reserved for patients with treatment failure or with suspected penicillin hypersensitivity. Further studies are required to establish the optimal dosages of omeprazole and amoxicillin (or other antibiotics), the frequency and the galenic formula (amoxicillin suspension or tablet?) of the constituents, as well as the relation to meals (pre- or postprandially) and the required minimal duration of treatment.

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