

# Randomised controlled trial of ranitidine versus omeprazole in combination with antibiotics for eradication of *Helicobacter pylori*

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Accepted September 1996

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## SUMMARY

**This study compared high dose ranitidine versus low dose omeprazole with antibiotics for the eradication of *H pylori*. 80 patients (mean age 48 years, range 18-75) who had *H pylori* infection were randomised in an investigator-blind manner to either a two-week regime of omeprazole 20 mg daily, amoxicillin 500 mg tid and metronidazole 400 mg tid (OAM), or ranitidine 600 mg bd, amoxicillin 500 mg tid and metronidazole 400 mg tid (RAM), or omeprazole 20 mg daily and clarithromycin 500 mg tid (OC), or omeprazole 20 mg daily and placebo (OP). *H pylori* was eradicated in 6 of 19 patients in the OAM group (32%); 8 of 18 in the RAM group (44%), 4 of 15 in the OC group (27%); none of 18 in the OP group (0%). [ $P < 0.005$  for OAM, RAM, OC vs OP;  $P = N.S.$  between OAM, RAM, OC]. Overall metronidazole resistance was unexpectedly high at 58%. Eradication rates in metronidazole sensitive patients were 71% (5/7) and 100% (3/3) for OAM and RAM respectively. In conclusion, *H pylori* eradication rates using high dose ranitidine plus amoxicillin and metronidazole may be similar to that of low dose omeprazole in combination with the same antibiotics or omeprazole with clarithromycin. Overall eradication rates were low due to a high incidence of metronidazole resistance but were higher in metronidazole-sensitive patients. Even high dose ranitidine with two antibiotics achieves a relatively low eradication rate. These metronidazole-based regimens cannot be recommended in areas with a high incidence of metronidazole resistance.**

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## INTRODUCTION

*Helicobacter pylori* infection is found in most patients suffering from chronic active gastritis or peptic ulceration.<sup>1</sup> Eradication of *H pylori* prevents relapses of duodenal ulcer<sup>1,2</sup> and probably lessens the risk of ulcer complications.<sup>3-6</sup>

The optimal therapeutic regimen for eradicating *H pylori* is not yet determined. Numerous studies have evaluated the combination of a proton pump inhibitor, omeprazole, with a single or double antibiotic regimen such as amoxicillin or clarithromycin, reporting eradication rates of around 80%.<sup>7-9</sup> In contrast, fewer studies have evaluated the role of histamine-2 receptor antagonists when combined with antibiotics. Hentschel et al<sup>10</sup> found that ranitidine in combination with amoxicillin plus metronidazole produced an eradication rate of 89%. Ranitidine

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combined with triple therapy (bismuth, metronidazole and tetracycline) produced an eradication rate of 84%.<sup>11</sup> Thus ranitidine in combination with antibiotics may be as effective as omeprazole plus antibiotics in the eradication of *H pylori*. However few randomised studies have compared ranitidine and antibiotics with omeprazole and antibiotics in the eradication of *H pylori*.

The aims of our study were to evaluate the efficacy of *H pylori* eradication using ranitidine compared to omeprazole when they are combined with antibiotics. The antibiotics used were amoxicillin and metronidazole to produce a triple therapy regimen without bismuth, as there is some evidence that the addition of bismuth is not necessary in achieving high eradication rates with this type of triple therapy.<sup>10</sup> These two regimens were compared to a control regimen of omeprazole alone and the regimen of omeprazole plus clarithromycin which has been associated with high eradication rates.

#### METHODS

The study was approved by the Research Ethical Committee of the Queen's University of Belfast and written informed consent was obtained from all patients.

80 dyspeptic patients who underwent upper gastrointestinal endoscopy and were found to have *H pylori* infection were studied. Patients were excluded if they were allergic to any of the study medication, pregnant or liable to become pregnant, lactating, had recent gastrointestinal haemorrhage, severe disease of any other kind or had taken antibiotics in the month before entry.

The presence of *H pylori* infection was assessed by endoscopy and antral biopsies were taken for histology and culture; rapid urease (CLO) test and the 13C-urea breath test (UBT) were also performed. *H pylori* infection was confirmed if at least two of the tests were positive. Two antral biopsies were taken for histology, and the presence of *H pylori* identified using a Giemsa stain. Two antral biopsies were taken for culture using non-selective medium of Columbia-based agar and selective medium (Dent's medium), incubated in micro-aerophilic conditions at 37°C for up to 10 days; then checked for metronidazole resistance in Columbia blood-agar with 5 mcg metronidazole disc incubated for 72 hours. One antral biopsy was taken for the CLO test (Delta West, Australia).

The 13C-urea breath test was performed according to the European 13C-urea breath test protocol and assessed by the Bureau of Stable Isotope Analysis Ltd., England. A positive result was taken as excess delta 13 C02 excretion > 5 per ml, standard delta notation.<sup>12</sup>

The patients were randomised in an investigator blind manner to a two-week regime of (1) omeprazole 20 mg daily, amoxicillin 500 mg tid and metronidazole 400 mg tid (OAM); (2) ranitidine 600 mg bd, amoxicillin 500 mg tid and metronidazole 400 mg tid (RAM); (3) omeprazole 20 mg daily and placebo (OP); or (4) omeprazole 20 mg daily and clarithromycin 500 mg tid (OC).

Repeat endoscopy for histology and culture and 13 C-UBT were undertaken 4 weeks after completion of therapy. Eradication of *H pylori* was considered successful if all three tests were negative.

Compliance was assessed by return tablet counts. Side-effect profile was determined by visits at two and six weeks after commencement of treatment, and patients were asked to contact the investigators if they had side-effects. Symptoms were assessed before treatment and four weeks after completing the treatment and graded by a scoring system. Patients were questioned in a standardised manner about five predefined symptoms: epigastric pain, nausea or vomiting, heartburn, postprandial discomfort or regurgitation. The presence of each symptom was scored as: 0-absent; 1 – recalled on direct questioning; 2-present but not impairing activities; 3-interfering with daily work and life. Frequency of symptoms was scored as: 1-one day or less per week; 2-several times each week; 3-daily. The scores were added for each patient giving a possible score ranging from 0 to 30.

The Chi-square test was used to compare the eradication rates between treatments; a P value of less than 0.05 was considered significant.

#### RESULTS

80 patients with *H pylori* infection entered the study. Their demographic and clinical details are summarised in Table 1. All four groups had similar demographic and clinical characteristics. Some of the patients had become asymptomatic at the time of the initial endoscopy.

Side effects occurred in two (10%) of the patients in the OAM group. One complained of nausea and rash and withdrew from the study, and another

TABLE I  
Patient demographic and clinical characteristics

	Omeprazole Amoxicillin Metronidazole (n=20)	Ranitidine Amoxicillin Metronidazole (n=20)	Omeprazole Placebo (n=20)	Omeprazole Clarithromycin (n=20)
Mean age (range) (y)	40 (18-75)	50 (18-65)	52 (26-82)	49 (28-75)
Men/women (n)	8/12	13/7	7/3	15/5
Diagnosis (n):				
Duodenal ulcer disease	14	14	17	12
Oesophagitis	3	1	3	5
Gastric ulcer	1	0	0	0
Normal	3	4	3	7
Median symptom score (range)	12 (0-23)	14 (0-22)	10 (0-22)	15 (0-30)
Smoker (n) (%)	4/7 (57%)	5/10 (50%)	3/12 (25%)	3/9 (33%)
Alcohol use (n) (%)	3/7 (43%)	7/9 (78%)	9/12 (75%)	7/9 (78%)

had diarrhoea but continued with the study. Two (10%) of the patients in the RAM group complained of nausea and vomiting and they both withdrew from the study. Two (10%) of the patients in the OP group complained of diarrhoea, one of whom withdrew from the study. Three (15%) of the patients in the OC group complained of diarrhoea (one) and vomiting (two); they all withdrew from the study. In total, 11% of patients suffered from side-effects and of these 9% withdrew from the study as a result.

Compliance was good in all the groups (>90% consumption of the delivered study medication) with no significant differences between them except for two patients who withdrew from the study because of poor compliance in the OC group. Compliance was 97% (range 86 - 100; n=12) in the OAM group; 94% (74 - 100; n=12) in the RAM group; 95% (72 - 100; n=13) in the OP group; 92% (72 - 100; n=8) in the OC group.

*H pylori* resistance to metronidazole was assessed. The metronidazole resistance was 50% (n = 7/14)

in the OAM group; 73% (11/15) in the RAM group; 60% (9/15) in the OP group; 47% (7/15) in the OC group. There was no significant difference in the metronidazole resistance between the groups. The overall metronidazole resistance was 58%.

The eradication of *H pylori* with the different regimens are summarised in Table II. The evaluable patient group includes the patients who completed the study and the intention-to-treat group includes all patients who participated in the study. The statistical results were the same for both evaluable and the intention to treat groups. The eradication rates with the regimens which included antibiotics were significantly higher than that for omeprazole alone (P<0.005). There were no significant differences in the eradication rates between the regimens which included antibiotics. In patients who had metronidazole sensitive *H pylori*, the eradication rates were 71% (5 out of 7) in the OAM group and 100% (3 out of 3) in the RAM group.

TABLE II  
*H pylori* eradication rates with the different regimens

Treatment	Evaluable (n; %)	Intention to treat (n; %)
Omeprazole Amoxicillin Metronidazole	6/19 (32%)	6/20 (30%)
Ranitidine Amoxicillin Metronidazole	8/18 (44%)	8/20 (40%)
Omeprazole Placebo	0/19 (0%)	0/20 (0%)
Omeprazole Clarithromycin	4/15 (27%)	4/20 (20%)

P,0.005 for all regimens with antibiotics versus omeprazole/ placebo.

No significant differences between regimens which included antibiotics.

## DISCUSSION

This study utilised the optimal design for an *H pylori* eradication study which is a randomised, investigator-blind, controlled design. We were stringent in our definition of eradication as we used three test methods – histology, culture, <sup>13</sup>C-urea breath test. *H pylori* was considered eradicated if all three tests were unable to detect it. In contrast, the recommendations regarding the definition of eradication relies on only two test methods<sup>13</sup> and some published studies only use one method.<sup>8, 14</sup> In addition to an efficacy analysis, we have also analysed our data on an intention-to-treat basis to avoid over-estimating the expected success of treatment used in routine clinical practice. This aspect has been neglected in many previous studies.<sup>7</sup> Our conclusions were the same regardless of the method of analysis.

At present it is uncertain which factor is more important for antimicrobial therapies using omeprazole-pH or antimicrobial activity. Omeprazole has intrinsic *in vitro* antimicrobial activity<sup>15, 16</sup> and may also improve the antimicrobial action of the co-administered acid-sensitive antibiotics when the intragastric pH approaches 7.<sup>17, 18</sup> We found that monotherapy with omeprazole did not eradicate *H pylori*,

confirming previous reports that omeprazole alone merely suppresses *H pylori* but does not eradicate it.<sup>19</sup>

The eradication rates achieved in this study were low compared to some previous similar studies. The eradication rates of ranitidine 1200 mg with amoxicillin plus metronidazole, and omeprazole 20 mg with the same antibiotics were 44% and 32% respectively. One group has found that the combination of omeprazole 40 mg daily with amoxicillin and metronidazole for 14 days gave an overall eradication rate of 91% but only 47% with metronidazole-resistant strains.<sup>20</sup> As the majority of our patients had metronidazole resistance, our results are similar to this group's eradication rates in those with metronidazole resistance. The only previous controlled randomised trial using ranitidine 300 mg daily in combination with amoxicillin and metronidazole for 10 days achieved an eradication rate of 89% which is comparable to that of bismuth triple therapy.<sup>10</sup> However their incidence of metronidazole resistance was low (11%) which could explain why they achieved higher eradication rates than us. Our eradication rate with omeprazole 20 mg daily and clarithromycin was low at 27% compared to previous studies which have found eradication rates of 63 to 80%.<sup>8, 9, 21, 22</sup> This could be explained by the low dose of omeprazole used in our study in contrast to omeprazole 40 mg daily which has been used in the other studies.

Although there may be a trend towards higher eradication rates in the ranitidine, amoxicillin and metronidazole group compared to omeprazole, amoxicillin and metronidazole (44% versus 32%), this lacked statistical significance because of the rather small sample size. However a study with the power to show clearly that a 12% difference was truly present or absent would have required a prohibitively high number of 400 subjects (power 80%).

Several other factors affect *H pylori* eradication. Compliance is important as eradication is low with poor compliance.<sup>23, 24</sup> The compliance of our patients was good, ranging from 92 to 97% and it would therefore seem unlikely that this factor would account for the low eradication rates in this study. Metronidazole resistance is associated with a marked reduction in eradication rates. We found an unexpectedly high prevalence of metronidazole resistance (58%) in this group of

patients. In comparison, the overall prevalence of metronidazole resistance in Europe is 28% with figures ranging from 7 to 49%.<sup>25</sup> This is the most likely explanation for the low eradication rates achieved with our regimens of metronidazole with amoxicillin and ranitidine or omeprazole. The reasons for the high prevalence of metronidazole resistance are uncertain. It could be speculated that there is a high usage of metronidazole in this community. Eradication rates increase with the total daily dose of omeprazole in combination with amoxicillin<sup>7</sup> and it may be that the low dose of omeprazole used in our study could have influenced the low eradication rates. The reason we used a low dose of omeprazole was to try to achieve comparable acid suppression with high dose ranitidine.

The frequency of side-effects found in this study (11%) is lower than that of triple therapy which includes bismuth, where the overall frequency of side-effects is 32%.<sup>7</sup> Our results are more comparable to the reported frequency of side-effects with omeprazole plus amoxicillin which is 11%. However the side-effects associated with our regimens appear to be more severe than bismuth triple therapy or omeprazole plus amoxicillin, as 9% withdrew from our study in consequence of side-effects compared to about 4% and 2% for the latter two regimens.<sup>7</sup>

Using the doses outlined in our study, a two-week regimen of omeprazole 20 mg daily plus amoxicillin and metronidazole would have cost £23.79 and ranitidine 1200 mg daily plus amoxicillin and metronidazole £56.25 (prices from British National Formulary, number 28, 1994). Thus using high dose ranitidine plus amoxicillin and metronidazole to eradicate *H pylori* does not give any definite cost/benefit advantage compared to low dose omeprazole with the same antibiotics. The most expensive regimen in this study was omeprazole with clarithromycin which cost £73.26.

In conclusion, *H pylori* eradication rates using high dose ranitidine plus amoxicillin and metronidazole may be similar to that of omeprazole in combination with the same antibiotics or clarithromycin. Eradication rates were probably low due to a high incidence of metronidazole resistance. The eradication rate was higher in metronidazole sensitive patients. Prior to using metronidazole-based regimens, the local metronidazole resistance rates should be

determined to ensure that efficacy is not compromised. Even if ranitidine plus amoxicillin and metronidazole had higher eradication rates than omeprazole with the same antibiotics (12% difference) undetected by the small sample size, the former regimen would still not have been as cost effective as the latter, and would have involved taking a larger number of tablets.

#### ACKNOWLEDGEMENTS

We are grateful to Dr Chris Patterson from the Department of Epidemiology and Public Health Medicine for advice on statistical analysis, Dr Michael Callender, Consultant Physician, for help with subject recruitment and Mr Barney O'Loughlin from the Department of Microbiology for performing the cultures for *H pylori*.

#### REFERENCES

1. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in Peptic Ulcer Disease. *JAMA* 1994; **272**: 65-9.
2. Tytgat G N J. Review article: Treatments that impact favourably upon the eradication of *H pylori* and ulcer recurrence. *Aliment Pharmacol Ther* 1994; **8**: 359-68.
3. Chung S C, Sung J Y, Hosking S W, et al. One week therapy for *H pylori* eradication: follow-up study of a randomized trial at one year after treatment. *Gastroenterology* 1993; **104**: Suppl. A56 (Abstract).
4. Graham D Y, Hepps K S., Ramirez F C, Lew G M, Saeed Z A. Treatment of *Helicobacter pylori* reduces the rate of rebleeding in peptic ulcer disease. *Scand J Gastroenterol* 1993; **28**: 939-42.
5. Labenz J & Borsch G. Role of *H pylori* eradication in the prevention of peptic ulcer bleeding relapse. Proceedings of the II United European Gastroenterology Week, Barcelona, 1993: A96 (abstract)
6. Rokkas T, Mavrogeorgis A, Rallis E, Giannikos N. *Helicobacter pylori* eradication reduces the possibility of rebleeding in peptic ulcer disease. Proceedings of the II United European Gastroenterology Week, Barcelona, 1993: A3 (Abstract).
7. Penston J G. *H pylori* eradication – understandable caution but no excuse for inertia. *Aliment Pharmacol Ther* 1994; **8**: 369 - 89.
8. Logan R P H, Gummett P A, Hegarty B T, Walker M W, Baron J H, Misiewicz J J. Clarithromycin and omeprazole for *Helicobacter pylori* (Letter). *Lancet* 1992; **340**: 239.
9. Logan R P H, Bardhan K D, Celestin L R, Theodossi A, Palmer K, Reed P I for the BHURG study. Clarithromycin (CL) and omeprazole (OM) in the prevention of duodenal ulcer (DU) recurrence and eradication of *H pylori* (Hp). *Am J Gastroenterol* 1994; **89**: 1378 (Abstract).

10. Hentschel E, Brandstatter G, Dragosics B, Hirschl A M, Nemec H, Schutze K, Taufer M, Wurzer H. Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter Pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 1993; **328**: 308-12.
11. Labenz J, Gyenes E, Ruhl G H, Börsch G. Amoxicillin plus omeprazole versus triple therapy for eradication of *Helicobacter pylori* in duodenal ulcer disease: a prospective, randomized, and controlled study. *Gut* 1993; **34**: 1167-70.
12. Logan R P H. Detection of *Helicobacter pylori* by the <sup>13</sup>C-urea breath test. In: Rathbone B J, Heatley R V, eds. *Helicobacter pylori* and gastroduodenal disease. Blackwell Scientific Publications, London, 1992; 88-106.
13. Korman M G, Marks I N, Hunt R H, Axon A, Blaser M J, McCarthy D M, Tytgat G N J. *Helicobacter pylori*: a workshop review. *Eur J Gastroenterol Hepatol* 1993; **5**: 963-7.
14. Peterson W L, Graham D Y, Marshall B, Blaser M J, Genta R M, Kleiln P D, Stratton C W, Drnec J, Prokocimer P, Siepman N. Clarithromycin as monotherapy for eradication of *Helicobacter pylori*: a randomized, double blind trial. *Am J Gastroenterol* 1993; **88**: 1860-4.
15. Suerbaum S, Laying H, Klemm K, Opferkuch W. Antibacterial activity of pantoprazole and omeprazole against *Helicobacter pylori*. *Eur J Clin Microbiol Infect Dis* 1991; **10**: 92-3 (Letter).
16. Bugnoli M, Bayeli P F, Rappuoli R, Pennatini C, Figura N, Crabtree J E. Inhibition of *Helicobacter pylori* urease by omeprazole. *Eur J Gastroenterol Hepatol* 1993; **5**: 683-5.
17. Paulsen O, Höglund P, Walder M. No effect of omeprazole-induced hypoacidity on the bioavailability of amoxicillin or bacampicillin. *Scand J Infect Dis* 1989; **21**: 219-23.
18. Goodwin C S, McNulty C A M. Bacteriological and pharmacological basis for the treatment of *Helicobacter pylori* infection. In: Rathbone B J, Heatley R V (eds). *Helicobacter pylori* and Gastroduodenal Disease, Blackwell Scientific Publications, London, 1992; 224-31.
19. Bayerdorffer E, Mannes G A, Sommer A, et al. High dose omeprazole treatment combined with amoxicillin eradicates *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 1992; **4**: 697-702.
20. Bell G D, Powell K U, Burrige S M, Bowden A N, Rameh B, Bolton G, Purser K, Harrison G, Brown C, Gant P W, Jones P H, Trowell J E. *Helicobacter pylori* eradication: efficacy and side effect profile of a combination of omeprazole, amoxicillin and metronidazole compared with four alternative regimens. *Q J Med* 1993; **86**: 743-50.
21. Schaufelberger H D, Logan R P H, Gummett P A. The effect of patients compliance on *Helicobacter*. Proceedings Digestive Disease Week, Barcelona 1993, A-104.
22. Greaves R G, Cayla R, Mendelson M G. Omeprazole versus clarithromycin and omeprazole for eradication of Hp. Proceedings Digestive Disease Week, Barcelona 1993, A-101.
23. Graham D Y, Lew G M, Klein P D, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. a randomized, controlled study. *Ann Int Med* 1992; **116**: 705-8.
24. Cutler A F, Schubert T T. Patient factors affecting *Helicobacter pylori* eradication with triple therapy. *Am J Gastroenterol* 1993; **88**: 505-9.
25. European Study Group on Antibiotic Susceptibility of *Helicobacter pylori*. Results of a multicentre European survey in 1991 of metronidazole resistance in *Helicobacter pylori*. *Eur J Clin Microbiol Infect Dis* 1992; **11**: 777-81.