Eradication of *Helicobacter pylori* with clarithromycin and omeprazole

R P H Logan, P A Gummett, H D Schaufelberger, R R F H Greaves, G M Mendelson, M M Walker, P H Thomas, J H Baron, J J Misiewicz

Abstract

Clarithromycin, a new and well tolerated, acid stable macrolide antibiotic, has a similar antimicrobial spectrum to erythromycin but a better in vitro MIC_{90} (0·03 $\mu g/l^{-1}$) against *Helicobacter pylori* (*H pylori*). This study aimed at determining the eradication rate using clarithromycin 500 mg thrice daily and omeprazole 40 mg daily for two weeks. Patients were given an endoscopy and *H pylori* status assessed by antral culture (microaerobic conditions, for up to 10 days), antral and corpus histology tests (haematoxylin and eosin/ Gimenez stains), and ^{13}C-urea breath test (^{13}C-UBT, European standard protocol, positive result=excess $\delta^{13}CO_2$ excretion >5 per mil). Compliance waa assessed by returned tablet counts. *H pylori* clearance at the end of treatment and eradication four weeks after finishing treatment were assessed by the ^{13}C-UBT. Seventy three patients (54 men, median age 45 years) with duodenal ulcers (n=42) or duodenitis/non-ulcer dyspepsia (n=31) all with a positive ^{13}C-UBT (mean (SEM) excess $\delta^{-13}CO_2$ excretion=26·6 (4·9) per mil) and either positive antral histology (n=72) or positive antral culture (n=35) were studied. Before treatment 2/27 (7%) isolates of *H pylori* were resistant to clarithromycin and five isolates were resistant to metronidazole. In 70/73 (96%) the ^{13}C-UBT was negative immediately after finishing treatment. Four weeks later the ^{13}C-UBT was negative in 57/73 (mean (SEM) excess $\delta^{13}CO_2$ excretion=1·2 (0·3) per mil, eradication rate=78%). Forty eight (66%) patients experienced a metallic taste while taking the tablets. Although four (5%) patients, however, could not complete the course of treatment, in only one of these four was *H pylori* not eradicated. These results show that duel therapy with clarithromycin and omeprazole is well tolerated. With an eradication rate of 78% it is an effective treatment for metronidazole resistant *H pylori* and may be an alternative to standard triple therapy.

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Parkside Helicobacter Study Group, Central Middlesex and St Mary's Hospitals, London
R P H Logan
P A Gummett
H D Schaufelberger
R R F H Greaves
G M Mendelson
M M Walker
P H Thomas
J H Baron
J J Misiewicz

Correspondence to:
Dr R P H Logan, Department of Gastroenterology and Nutrition, Central Middlesex Hospital, Acton Lane, Park Royal, London NW10 7NS.

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Eradication of *Helicobacter pylori* (*H pylori*) cures gastritis and prevents relapse of duodenal ulcer.[1] There are several drawbacks, however, to the recommended two week triple therapy for eradicating *H pylori*.[2] Bismuth salts, an important component of most regimens are not universally available, while failure of eradication therapy is often associated with pretreatment metronidazole resistant *H pylori*.[3,4] Poor compliance with treatment because of side effects, frequent dosing, and the length of treatment is also a factor.[5] Simpler and better tolerated regimens that contain neither bismuth nor metronidazole are needed.

Omeprazole, a H^+/K^+ ATPase inhibitor, has been proposed as a suitable adjunct to *H pylori* treatment regimens for several reasons. It seems to suppress *H pylori* directly[6-8] and to increase the antibacterial effectivness of some antibiotics by increasing the gastric pH towards their negative logarithms of the acidic dissociation constant (pKa). Omeprazole may also decrease the acid storage pool for weak base antibiotics (thus increasing the gastric mucosal concentration)[9] and may decrease the rate of intragastric catabolism of the antimicrobial.

Clarithromycin (Abbott Laboratories, North Chicago, Illinois) is a new macrolide antibiotic (6-methoxy-erythromycin) with similar antimicrobial spectrum to erythromycin, but is more acid stable with fewer alimentary side effects. It has more predictable pharmacokinetics and has a half life of eight hours.[10] Clarithromycin is used for the treatment of upper and lower respiratory tract infections and at doses of 2 g twice daily has been shown to be effective in HIV positive patients with *Mycobacterium avium* complex infections. In vitro its MIC_{90} against *H pylori* is 0·03 $\mu g\ ml^{-1}$. To develop a regimen that contains neither bismuth, nor metronidazole, we have assessed the effectiveness of two weeks treatment with clarithromycin 500 mg thrice daily and omeprazole 40 mg in the morning in eradicating *H pylori*.

Patients and methods

After routine diagnostic upper gastrointestinal endoscopy, patients with known *H pylori* infection were invited to enter the study, which was approved by the Parkside ethical committee. The patients gave written informed consent. Patients with previous gastric surgery, known bleeding diathesis, penicillin allergy, or taking oral anticoagulants were excluded.

All endoscopes were disinfected after each examination using an automatic washing machine (Olympus EW20) and the biopsy forceps were sterilised by autoclaving.[11]

ASSESSMENT OF *H PYLORI* STATUS

H pylori status was determined using the ^{13}C-urea breath test (^{13}C-UBT, see over) and histological examination (two antral biopsy specimens processed to paraffin wax, haematoxylin and eosin and Gimenez stains). Whenever possible, after initial isolation (two antral and two corpus biopsy specimens, selective and

non-selective media, microaerobic conditions for up to 10 days), pure cultures were harvested and stored in 10% glycerol broth at −80°C. Tests for metronidazole and clarithromycin sensitivity were then done using an in vitro disk method (Mast sensitivity disks (5 μg), Mast Laboratories, Liverpool; Sensi disks (1 μg), Beckton Dickenson Microbiological Systems, Cockeysville, MD, USA).

Patients were classified as *H pylori* positive by a positive ^{13}C-UBT and positive histoligical tests or culture. Clearance of *H pylori* was defined as a negative ^{13}C-UBT (excess $\delta^{13}CO_2$ excretion <5 per mil) at the end of treatment, while eradication was defined as a negative ^{13}C-UBT one month or longer after the end of treatment.

^{13}C-UREA BREATH TEST

The ^{13}C-UBT (European Standard Protocol)[12] was done within two days of the initial endoscopy in all patients. Briefly, a baseline sample of expired breath was collected before drinking a fatty liquid test meal (76% lipid, 19% carbohydrate, 5% protein) to delay gastric emptying. After 10 minutes, ^{13}C-urea 100 mg (99% pure, Cambridge Isotopes, Boston, Mass) in 50 ml of tap water was swallowed and distributed within the stomach by turning the patient to the left and right decubitus position. Two litre serial breath samples were collected every five minutes into a large reservoir collecting bag, from which a single 20 ml aliquot was taken at the end of the test and analysed by mass spectrometry (Bureau of Stable Isotope Analysis, Brentford, London). A positive result was defined as excess $\delta^{13}CO_2$ excretion >5 per mil, as determined from previous studies.[12]

TREATMENT

Patients with a positive ^{13}C-UBT, and positive histological tests or positive culture, or both, were given omeprazole 40 mg each morning and clarithromycin 500 mg thrice daily for 14 days. Patients were forewarned of possible taste disturbance. The dose and frequency of the regimen was based on the half life of clarithromycin and facilitating patient compliance.

FOLLOW UP

A second ^{13}C-UBT was done immediately after completing treatment, when compliance and side effects were assessed by returned tablet count and direct questioning. A third ^{13}C-UBT was done one month later, with a negative result taken to point to successful eradication. In patients in whom *H pylori* was not eradicated, repeat endoscopy with biopsy specimens and cultures were done to determine if treatment failure was a result of the development of clarithromycin resistance.

Results

Seventy three patients (36 men, median age 46 years, range 29–68, with either active or previous duodenal ulcers (n=42) or dyspepsia with endoscopic duodenitis/non-ulcer dyspepsia (n=31)) all with a positive ^{13}C-UBT (mean (SEM) excess $\delta^{13}CO_2$ excretion=26·6 (4·9) per mil) and either positive antral histology (n=72) or positive antral culture (n=35) were studied. Twenty five (34%) patients had previously received anti-*H pylori* treatment[3 13] but had failed to eradicate the infection.

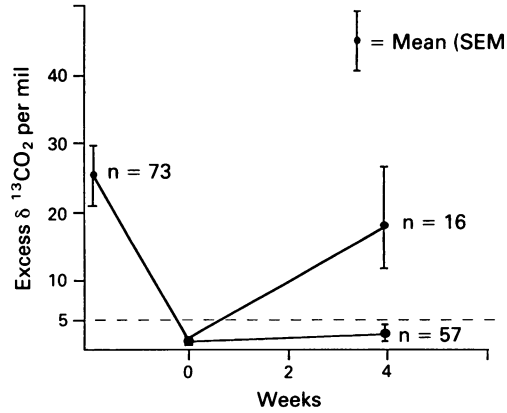
In 70/73 (96%) the ^{13}C-UBT was negative immediately after finishing treatment. Four weeks after the end of treatment the ^{13}C-UBT was negative in 57/73 (mean (SEM) excess $\delta^{13}CO_2$ excretion=1·2 (0·3) per mil) eradication rate=78%, intention to treat analysis, Figure). *H pylori* was not eradicated in 16 patients, including one patient who took the drugs for only three days. In those patients in whom *H pylori* had failed previous treatments (n=25), eradication was achieved in 16/25 (64%) compared with 41/48 (85%) of those who had not been previously treated (χ^2=4·4, p=0·04).

Forty eight patients (48/73, 66%) experienced a dry metallic taste while taking the tablets, which prevented three patients from completing the course of treatment; in one patient severe taste disturbance occurred within three days of starting treatment. In the remaining patients taste disturbance resolved completely within days of finishing treatment and did not impair compliance or eradication. Other side effects occurred infrequently (7%) and included nausea, headache, and oral candidiasis. No patient experienced diarrhoea.

ANTIBIOTIC SENSITIVITIES

Before treatment positive cultures were obtained from 35/51 patients studied. Of 27 available isolates, 25/27 (93%) were sensitive to clarithromycin while in five patients isolates of *H pylori* were resistant to metronidazole. *H pylori* was eradicated in both patients with pretreatment clarithromycin resistant strains and in 4/5 patients with metronidazole resistant strains.

Comparison of before and after treatment isolates from 8/16 available culture showed acquired clarithromycin resistance in one of five patients with persistent *H pylori*. *H pylori* could not be adequately cultured in three further patients who failed treatment.



^{13}C-urea breath test results showing the effect of two weeks clarithromycin 500 mg thrice daily and omeprazole 40 mg in the morning, before and at 0 and four weeks after finishing treatment (=eradication). (Positive result=excess $\delta^{13}CO_2$ excretion >5 per mil.)

Discussion

This new combination of the powerful acid inhibitor omeprazole and an antibiotic (dual therapy) has both theoretical and practical advantages over standard triple therapy for eradicating *H pylori*. It is a logical, rational first line 'curative' treatment of duodenal ulcer with excellent compliance because it is well tolerated and uses less than half the tablets of two weeks triple therapy. Our results suggest that the new dual therapy using omeprazole and clarithromycin may be an effective alternative to triple therapy for eradicating *H pylori*.

The in vitro activity of erythromycin against *H pylori* is comparable with other antibiotics, but its prokinetic activity (causing side effects) and poor acid stability have limited its use in the treatment of *H pylori*. The newer macrolide antibiotics were designed to overcome the parent compound's drawbacks and are active in vitro against *H pylori*, but only clarithromycin is also active in vivo. Indeed results to date suggest that clarithromycin is the most effective anti-*H pylori* drug available at present.[14 15] In a preliminary study of single drug therapy Graham found clarithromycin 250 mg four times daily for two weeks eradicated *H pylori* in 6/14 (42%) subjects,[14] while Neri *et al* found that clarithromycin (250 mg four times daily) combined with colloidal bismuth subcitrate (120 mg four times daily) for two weeks increased the eradication rate to 52%.[16] The high eradication rate achieved in our study by clarithromycin with omperazole is probably because of the lower MIC_{90} of clarithromycin and its active 14-hydroxy metabolite at the higher pH produced by omeprazole. The intrinsic *H pylori* suppressive properties of omeprazole, however, may also have been important.[17-19] Primary and acquired resistance to macrolides is a recognised problem and may also occur with clarithromycin, making further studies of treatment with clarithromycin alone unlikely.

Similar encouraging results to our own have been reported with omeprazole and amoxycillin duel therapy.[20] Several groups have failed, however, to duplicate the initial encouraging results; our results show an eradication rate of 28% with variable results (43%–0%) reported by others.[21-24] Unge *et al* using omeprazole 40 mg in the morning and amoxycillin 750 mg twice daily found an overall eradication rate of 54% although in compliant patients (<33% of study population) the eradication rate was 74%.[24]

The eradication rate of the omeprazole and clarithromycin dual therapy recorded in this study compares favourably with that of standard triple therapy. Although the eradication rate was lower in patients previously treated for *H pylori*, this did not seem to be because of differences in patient compliance or antimicrobial sensitivity and was not seen in previous studies.[3 13 21]

At the comparatively high doses, similar to those used in this study, clarithromycin may cause a metallic taste (manufacturer's data). Patients were therefore warned of this before starting treatment and although 66% had a transient taste disturbance, over 95% could complete the regimen successfully and eradicate *H pylori*. Only one patient had this side effect immediately and intolerably, possibly an idiosyncratic response, but the importance of taste disturbance varies between different people and ethnic groups.

In this study 93% of the strains of *H pylori* studied were initially sensitive to clarithromycin, but in one of the five patients in whom treatment failed the bacteria had become resistant to clarithromycin. Resistance to clarithromycin may arise less readily than to imidazoles,[25] but more data are needed to quantify this problem and suggest preventative methods. Further studies are also needed to optimise the dose and duration of clarithromycin and an appropriate antisecretagogue.

In clinical practice this dual therapy of omeprazole and clarithromycin may provide an effective alternative first line anti-*H pylori* treatment in populations where the prevalence of imidazole resistant *H pylori* is high. We currently use this regimen as first line treatment for patients with known metronidazole resistant *H pylori* and as second line treatment after failure of standard triple therapy.

Preliminary results of this study were presented as an abstract to the British Society of Gastroenterology in September 1992. The authors thank the medical and endoscopy staff of both Hospitals for their help and cooperation, and Abbott Laboratories for their support.

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