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Incidence of duodenal ulcer healing after 1 week of proton pump inhibitor triple therapy for eradication of Helicobacter pylori

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SUMMARY

Background: A number of clinical studies have assessed the efficacy of short-term twice-daily *Helicobacter pylori* eradication regimens but few have investigated the proportion of patients in whom duodenal ulcer disease was healed with these regimens.

Aim: To compare the safety and efficacy of four 1-week *H. pylori* eradication regimens in the healing of *H. pylori* associated duodenal ulcer disease.

Methods: Following endoscopic confirmation of duodenal ulcer disease and a positive CLO test, patients underwent a ^{13}C-urea breath test to confirm *H. pylori* status. Treatment with one of four regimens: LAC, LAM, LCM or OAM, where L is lansoprazole 30 mg b.d., A is amoxycillin 1 g b.d., M is metronidazole 400 mg b.d., C is clarithromycin 250 mg b.d., and O is omeprazole 20 mg b.d., was assigned randomly to those patients who were *H. pylori* positive, with 62 (LAC), 64 (LAM), 61 (LCM) and 75 (OAM) patients in each treatment group. Follow-up breath tests and endoscopies were performed at least 28 days after the end of treatment.

Results: Duodenal ulcer disease was healed 28 days after treatment in 53/62 (85.5%) patients who were treated with LAC, 52/64 (81.3%) of patients treated with LAM, 49/61 (80.3%) of patients treated with LCM and 60/75 (80.0%) of patients treated with OAM (intention-to-treat analysis, $n = 262$, assumed unhealed if no follow-up endoscopy was performed). All the treatments were of similar efficacy ($P = 0.85$, chi-squared test) with regard to the healing of duodenal ulcer disease.

Conclusions: The four 1-week treatment regimens were equally effective in healing *H. pylori* associated duodenal ulcer disease.

INTRODUCTION

Since the identification of *Helicobacter pylori* as a causative factor in the development of duodenal ulcer disease, it has been shown that eradication of the bacterium results in healing and prevention of relapse of duodenal ulcers[1–4].

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A large number of studies have attempted to define the best drug combinations and durations for eradication of *H. pylori* infection. The most consistently successful and patient-friendly eradication regimens have been those which combine a proton pump inhibitor with two antimicrobials; such treatment needs to be given for only 1 week in order to eradicate *H. pylori* in about 90% of patients.[5–10] However, to our knowledge, there have been no studies published to date which report the proportion of patients in whom duodenal ulcer disease is healed, when the initial *H. pylori* eradication therapy is given for only 1 week, with no additional acid

suppressive therapy before or following the triple therapy. This study investigated the efficacy of a treatment regimen administered for only 1 week in healing duodenal ulcer disease. The treatment was not supplemented by continued acid suppression following completion of the 1-week triple therapy regimen.

This study was part of a larger investigation which was initiated in order to measure the efficacy of four treatment regimens comprising a proton pump inhibitor plus two antibiotics, all given twice daily for 1 week, in the eradication of *H. pylori* in patients suffering from either duodenal ulcer or gastritis. This study concluded all four treatment regimens were safe and effective in eradicating *H. pylori* in the patient population studied. LAC was the most efficacious treatment in patients with pretreatment metronidazole resistant *H. pylori*, and was significantly better than LAM and OAM in this group of patients.[9] The subanalysis described here deals with the relative efficacies of these four treatments in the healing of *H. pylori* associated duodenal ulcer disease.

PATIENTS

H. pylori positive patients with duodenal ulcer disease were recruited as part of a larger study,[9] which also included patients with *H. pylori* associated gastritis. This was a multicentre, single-blind, prospectively randomized, parallel group study, carried out between November 1994 and May 1995 in 55 hospitals in the UK and Ireland.

H. pylori positive patients of either gender aged between 18 and 80 years inclusive, with endoscopic evidence of a duodenal ulcer (defined as a break in the mucosal surface with slough at the base) were invited to participate in the study. Exclusion criteria were treatment with proton pump inhibitors, bismuth-containing compounds or antibiotics within the 2 weeks prior to study entry or allergy to any of the study drugs. Patients were not permitted to take H_2-receptor antagonists, any other ulcer healing drugs or non-steroidal anti-inflammatory drugs (except for aspirin taken as anti-platelet prophylaxis) whilst receiving study medication. Previous gastric surgery, a clinically significant gastrointestinal haemorrhage in the previous month, concomitant gastric ulcer, severe oesophagitis (Grade II or higher), Barrett's oesophagus or inflammatory bowel disease also precluded entry into the study.

METHODS

Determination of H. pylori *status*

One antral biopsy was taken for the CLO test. A further six biopsies were taken at the baseline endoscopy for histological examination (two antral and two corpus) and microbiological culture (two antral).

Patients in whom the CLO test was positive were invited to undergo a ^{13}C-urea breath test (Bureau of Stable Isotope Analysis, Brentford, UK) to confirm *H. pylori* status.[11] Patients were considered to be *H. pylori* positive if they had a positive ^{13}C-urea breath test and at least one positive test from histological and microbiological investigation. Patients who did not fulfil this definition of being *H. pylori* positive were not eligible to enter the study.

Treatment

Patients were randomized to one of the following treatment regimens according to a computer generated list stratified by investigator in blocks of four patients: lansoprazole 30 mg b.d., amoxycillin 1 g b.d., metronidazole 400 mg b.d. (LAM); lansoprazole 30 mg b.d., amoxycillin 1 g b.d., clarithromycin 250 mg b.d. (LAC); lansoprazole 30 mg b.d., clarithromycin 250 mg b.d., metronidazole 400 mg b.d. (LCM); omeprazole 20 mg b.d., amoxycillin 1 g b.d., metronidazole 400 mg b.d. (OAM).

Treatment was dispensed in 7-day blister packs. Each blister contained all three drugs to be taken at each dosing time. All medication was taken 30 min before breakfast and the evening meal every day.

Assessments

Patients returned to the clinics *at least* 28 days after completing the treatment, when they underwent a ^{13}C-urea breath test and endoscopy. If a patient had had more than one ulcer reported at baseline, all ulcers had to be healed at follow-up endoscopy in order to classify the patient as healed.

Statistical analysis

Since the relative proportions of patients recruited having duodenal ulcer and/or non-ulcer gastritis were unknown at the start of the study, statistical calculations were performed in order to ascertain the number

of patients needed to show equivalence between LAM and OAM with respect to *H. pylori* eradication, regardless of initial diagnosis. On the assumption that 80% of patients treated with LAM and OAM would have their *H. pylori* eradicated, it was calculated that 112 patients per treatment arm would be required to show equivalence within 15% with a power of 80% at a 5% level of significance (two-tailed).

Two patient populations were identified for analysis of efficacy. The per protocol population was defined as all patients with a duodenal ulcer who had had a positive breath test at study entry who had not had treatment with a proton pump inhibitor within 14 days of study entry, who had taken no forbidden concurrent medication during the study and had taken at least 70% of study medication and returned for a follow-up endoscopy and breath test. The intention-to-treat population was defined as all patients who had had a positive breath test at study entry and who had taken at least one dose of study medication. Patients who had no follow-up endoscopy results were assumed to be unhealed.

Treatment groups were compared with respect to the proportion of patients in whom duodenal ulcer had healed using a chi-squared test.

A safety analysis was carried out on all patients who entered the study, which compared treatments with respect to maximum severity of the reported clinical adverse events using the Kruskal–Wallis test. These data have been reported elsewhere[9] and will not be referred to in this analysis.

The study was approved by the local Ethics Committee at each participating centre and written informed consent was obtained from patients prior to entering the study.

RESULTS

Efficacy

Two hundred and sixty-nine *H. pylori* positive patients with duodenal ulcer entered the study, of whom 234 were eligible and evaluable for the per protocol analysis and 262 were eligible for the intention-to-treat analysis of duodenal ulcer healing status. Seven patients were deemed ineligible as a result of negative or inconclusive ^{13}C-urea breath tests. Clinical characteristics of the 262 eligible intention-to-treat patients are summarized in Table 1. Most of the patients (79%) had only one ulcer at baseline and only 16 patients had three or more ulcers. The diameter of the ulcers reported varied from < 5 mm to ≥ 21 mm. Most patients ($n = 149$, 56.9%) had ulcers of diameters between 5 and 10 mm.

Table 2 summarizes the reasons for inevaluability of the 28 patients who were excluded from the per protocol analysis.

Ulcer healing 28 days after treatment

The proportion of patients in whom duodenal ulcer disease was healed is shown in Table 3 for both patient populations. There was no significant difference

Table 1. Clinical characteristics of eligible patients

	Treatment Group			
	LAC $n = 62$	LAM $n = 64$	LCM $n = 61$	OAM $n = 75$
Mean age (years)	45.9	47.4	49.3	46.7
Range	22–75	21–68	27–77	21–74
Gender				
Male *n* (%)	42 (68)	46 (72)	37 (61)	52 (69)
Female *n* (%)	20 (32)	18 (28)	24 (39)	23 (31)
Smoking				
Non-smoker *n* (%)	15 (24)	19 (30)	21 (34)	20 (27)
Ex-smoker *n* (%)	14 (23)	13 (20)	10 (17)	6 (8)
Smoker *n* (%)	33 (53)	32 (50)	30 (49)	49 (65)
No. of ulcers *n* (%)				
1	43 (69)	53 (83)	51 (84)	61 (81)
2	15 (24)	7 (11)	5 (8)	11 (15)
$\geqslant 3$	4 (7)	4 (6)	5 (8)	3 (4)

Table 2. Reasons for exclusion from per protocol population

	Treatment group			
	LAC	LAM	LCM	OAM
Failed to attend Visit 3	0	3	2	3
Adverse event	0	0	0	3
Proton pump inhibitors taken	0	3	0	0
Visit 3 breath test < 28 days post-treatment	0	3	3	4
No breath test done or result inconclusive at Visit 3	2	0	0	2

between the treatment groups with respect to the healing of duodenal ulcers in either the per protocol (chi-squared test, $P = 0.91$) or the intention-to-treat ($P = 0.85$) populations. In 28 patients in whom duodenal ulcers healed, *H. pylori* infection persisted despite triple therapy. Of the 23 patients who were unhealed at follow-up endoscopy, 12 remained *H. pylori* positive and 11 were *H. pylori* negative as judged by the ^{13}C-urea breath test (Table 3).

DISCUSSION

This study has shown that a 1-week treatment for *H. pylori* eradication results in healing of duodenal ulcer disease in most patients. This is in contrast to acid suppression alone: H_2-receptor antagonists take 8 weeks or more and proton pump inhibitors take 4 weeks to heal duodenal ulcers. However, the data also show that in some patients, the ulcer heals even if *H. pylori* is not eradicated, or vice versa.

H. pylori was eradicated and duodenal ulcers were healed in this study by using a short and simple dosing regimen of a proton pump inhibitor and two antibiotics, thus confirming previous studies in which similar 7-day treatment regimens were used.[7, 10] Treatment with 'classic' triple therapy (bismuth plus two antibiotics) has also been shown to heal duodenal ulcer disease when administered for only 1 week[12, 13] although it should be noted that the dosage regimens used in these latter studies were more complicated than the twice daily dosing of a proton pump inhibitor plus two antibiotics.

It is interesting to note that ulcers were healed in 28 of 40 patients in whom *H. pylori* was not eradicated. This finding is consistent with those of other investigators, who found that the number of patients in whom *H. pylori* was eradicated was lower than the number in whom duodenal ulcer had healed.[2, 7, 13, 14] The healing of ulcers in patients in whom *H. pylori* is not eradicated could be a result of very marked acid suppression achieved by the proton pump inhibitors, which were given at double the usual duodenal ulcer healing dose.

Table 3. Duodenal ulcer healing 28 days after treatment

	Treatment group			
	LAC	LAM	LCM	OAM
*Per protocol**				
Healed *n* (%)	52 (88)	46 (92)	46 (89)	54 (90)
95% Cl (healing rate)	76.5, 94.7	79.9, 97.4	75.9, 95.2	78.8, 95.9
H. pylori negative *n*	49	38	40	48
H. pylori positive *n*	3	8	6	6
Unhealed *n* (%)	7 (12)	4 (8)	6 (12)	6 (10)
H. pylori negative *n*	4	0	4	3
H. pylori positive *n*	3	4	2	3
Intention to treat†				
Healed *n* (%)	53 (86)	52 (81)	49 (80)	60 (80)
95% Cl (healing rate)	73.7, 92.7	69.2, 89.5	67.8, 89.0	68.9, 88.0
H. pylori negative *n*	50	41	42	53
H. pylori positive *n*	3	11	7	7
Unhealed *n* (%)	7 (12)	4 (7)	6 (11)	6 (9)
H. pylori negative *n*	4	0	4	3
H. pylori positive *n*	3	4	2	3

*13 missing endoscopies (LAC = 1, LAM = 5, LCM = 4, OAM = 3).
†25 missing endoscopies (LAC = 2, LAM = 8, LCM = 6, OAM = 9), assumed unhealed.

Healing could also be due to suppression of *H. pylori* during, or after, the treatment. Logan *et al.*[15] demonstrated that proton pump inhibitor treatment of *H. pylori* positive patients results in suppression of *H. pylori* coupled with a decrease in antral and an increase in fundic colonization. The resultant clearance of *H. pylori* from the antrum and the concomitant decrease in antral gastritis may be responsible for the healing of duodenal ulcers in those patients who were not successfully eradicated of their *H. pylori* infection. This hypothesis is supported by the observation that suppression of *H. pylori* infection decreases basal and stimulated acid secretion in patients with duodenal ulcer disease,[16] thus providing conditions favouring ulcer healing.

Whilst failure of *H. pylori* eradication therapy may still be accompanied by ulcer healing, it also appears that successful eradication may co-exist with persistence of the ulcer crater. These results suggest that some duodenal ulcers may not be dependent on *H. pylori*. The results of this study further indicate that it cannot be assumed that ulcer healing and *H. pylori* eradication are invariably associated with one another. In some circumstances it may therefore be important that ulcer healing and *H. pylori* eradication are verified independently after a course of anti-*H. pylori* treatment.

In conclusion, this large multicentre randomized study has demonstrated that 1 week of treatment with a proton pump inhibitor and two antibiotics will heal about 80% of *H. pylori* associated duodenal ulcers.

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