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Patient factors that predict failure of omeprazole, clarithromycin, and tinidazole to eradicate *Helicobacter pylori*

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Abstract: Omeprazole (20mg od/b.d.), clarithromycin (250mg b.d.) and tinidazole (500mg b.d. for 7 days) [OCT] is an effective regimen against *Helicobacter pylori*. However, treatment fails in 5%–10% of patients and the reasons for this are not clear. We investigated patient factors that independently predicted failure of this regimen. *H. pylori*-positive patients were prescribed OCT and the success of treatment was evaluated by the ^{13}C-urea breath test at least 4 weeks after completion of therapy. Patients were prospectively interviewed on past medical history of peptic ulcer and H_2-receptor antagonist (H_2RA) pre-treatment, smoking history, and alcohol intake. Data were also collected on age, gender, and endoscopic diagnosis to determine factors predicting failure of OCT. *H. pylori* eradication was achieved in 238 of 273 patients [87%–95% confidence intervals (CI), 83%–91%]. Age, alcohol intake, past medical history of peptic ulcer and peptic ulcer at endoscopy were not independently associated with treatment failure. *H. pylori* eradication with OCT was less successful in women ($P = 0.02$), in patients who had received H_2RA pre-treatment ($P = 0.02$), and in smokers ($P = 0.02$) when evaluated by multiple logistic regression. These findings indicate that OCT is less effective in smokers and in patients who receive H_2RA pre-treatment suggesting that these agents should be avoided, if possible, before the patient commences therapy. *H. pylori* eradication was less successful in women; this result needs further evaluation.

Key words: *Helicobacter pylori*, eradication, smoking, gender, H_2 receptor antagonist

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Introduction

The most effective therapy for *Helicobacter pylori* gastritis is still a subject of intense debate. Omeprazole (20mg od), clarithromycin (250mg b.d.), tinidazole (500mg b.d.) [OCT] has emerged as one of the most promising regimens, achieving eradication rates of 90%–95%.[1,2] Treatment still fails in 5%–10% of patients, however, and the reasons for this are unclear.

OCT contains a 5-nitroimidazole moiety and other regimens using this antibiotic are less effective against 5-nitroimidazole-resistant strains of *H. pylori*.[3,4] We have shown, however, that OCT is effective against 5-nitroimidazole-resistant *H. pylori*, so this factor is unlikely to explain treatment failure.[5] OCT may be less effective against *H. pylori* strains resistant to clarithromycin, but this occurs in less than 5% of the population we studied.[5]

Compliance is a major factor in determining treatment of OCT failure,[6] but this regimen is simple to take and is associated with few adverse events, resulting in good compliance. In published studies of OG, all patients have taken more than 90% of their medication,[1,5,7] so lack of compliance is unlikely to be a major reason for OCT failure. Other patient factors such as age, omeprazole pre-treatment, and smoking history,[8] have been shown to effect the efficacy of omeprazole and amoxycillin in treating *H. pylori* infection. It is possible that patient factors may also be important in determining the efficacy of OCT, and we aimed to investigate this further.

Methods

Patients attending an open-access dyspepsia service had upper gastrointestinal endoscopy. *H. pylori* infection was assessed by ^{13}carbon-urea breath test (^{13}C-UBT), histology, microbiology, and/or rapid urease test. An

experienced histopathologist carried out histological examination of two antral and two corpus biopsies, using a modified Giemsa stain. One antral biopsy was added to a 10% urea solution with two drops of phenol red to act as a rapid urease test and evaluated at 24h. A further antral biopsy was cultured under microaerophilic conditions with selective and non-selective media for 7 days. The ^{13}C-UBT was carried out according to standard protocols,[9] using 4g citric acid with 200ml of water as a test meal and 100mg of ^{13}C-labeled urea (Cambridge Isotopes, Boston, Mass., USA; 99% pure). Breath samples were obtained at 0 and 30min and analyzed using a mass spectrometer (ABCA-NT; Europa Scientific). Patients were defined as infected with *H. pylori* if the ^{13}C-UBT and at least one of the three biopsy tests were positive. *H. pylori*-positive patients were prescribed omeprazole (20mg od/b.d.), clarithromycin (250mg b.d.), and tinidazole (500mg b.d.) for 7 days and treatment success was evaluated by ^{13}C-UBT at least 4 weeks after completion of therapy. All patients took more than 90% of the medication prescribed, as determined by return tablet count and patient interview. Written informed consent was obtained from all patients.

Information on factors that might predict treatment failure was prospectively obtained by patient interview. Data on age, fender, endoscopic diagnosis, past history of peptic ulcer, smoking history, alcohol intake, and previous H_2 receptor antagonist (H_2RA) intake were collected. Patients were defined as having had H_2RA pre-treatment if they had taken these drugs for at least 1 month and had last taken these drugs within 2 days of receiving eradication therapy. A proportion of patients in this study were involved in a trial on the efficacy of OCT.[5] Patients who had had previous eradication therapy and those who had taken proton pump inhibitors (PPI) or bismuth salts, antibiotics, or PPI within 1 month of entry into the study were excluded.

Statistical analysis

The factors above were compared in patients in whom *H. pylori* eradication was successful and in those in whom treatment failed, using SPSS for Windows V 6.1. Age, alcohol, and smoking were compared using a two-tailed Student's *t*-test. H_2RA pre-treatment, gender, past medical history of peptic ulcer, and endoscopic diagnosis were compared using Fisher's exact test. Factors shown by these analyses to be associated with treatment failure were assessed by multiple logistic regression.

Results

Two hundred and seventy-three patients were evaluated; age (mean ± SD) was 49.7 ± 13.4 years (range 20–78 years) and 157 (58%) were male. The patients smoked a mean of 7.8 ± 10.7 cigarettes per day and consumed 9.7 ± 13.9 units of alcohol per week. Sixty-seven (24.5%) patients had received H_2RA pre-treatment (40 ranitidine, 26 cimetidine, and 1 famotidine), 13 (5%) had been treated with non-steroidal anti-inflammatory drugs (NSAIDs), and 78 (29%) had a past medical history of peptic ulcer. Diagnoses at endoscopy were; normal (n = 127), duodenitis (n = 68), duodenal ulcer (n = 28), gastric ulcer (n = 8), esophagitis (n = 18), and miscellaneous (n = 24). In clinical practice, *H. pylori* eradication is not indicated in patients with normal endoscopy findings, but this was undertaken in the context of a clinical trial. *H. pylori* eradication was successful in 238 of the 273 patients (87%; 95% CI, 83%–91%), with 35 treatment failures.

Patient factors were compared in the successful treatment and failed treatment groups (Table 1). Age, peptic ulcer at endoscopy, and alcohol intake were not associated with treatment failure. Smoking history, H_2RA pre-treatment, and past medical history of peptic ulcer

Table 1. Success of *H. pylori* eradication therapy according to patient factors

	ST (n = 238)	FT (n = 35)	Two-tailed P value
Age (years)	50.0 ± 13.5	48.4 ± 13.3	0.51*
Alcohol (units per week)	9.8 ± 13.0	8.8 ± 19.2	0.71*
Smoking (cigs per day)	7.2 ± 10.1	12.3 ± 13.7	0.008*
H_2RA pre-treatment	n = 49 (21%)	n = 18 (51%)	<0.0002**
Female	n = 96 (40%)	n = 20 (57%)	0.06**
Peptic ulcer	n = 33 (14%)	n = 3 (9%)	0.53**
PMH peptic ulcer	n = 62 (26%)	n = 16 (46%)	0.02**

*Student's *t*-test; **Fisher's exact test

ST, successful treatment; FT, failed treatment; PMH, past medical history; H_2RA, H_2 receptor-antagonist

Table 2. Multiple logistic regression on patient factors associated with OCT failure

	Two-tailed *P* value	Odds ratio	95% CI of odds ratio
Female gender	0.022	0.64	0.94–0.43
H_2RA pre-treatment	0.016	0.59	0.84–0.42
Smoking	0.019	0.62	0.92–0.42
PMH peptic ulcer	0.25	0.76	1.2–0.5

CI, Confidence intervals

were significantly increased in patients in whom treatment failed, while female gender was marginally associated with unsuccessful eradication. To determine factors that were independently associated with failed eradication, smoking history, H_2RA pre-treatment, past medical history of peptic ulcer, and gender were analyzed by logistic regression. This indicated that smoking and H_2RA pre-treatment remained significantly associated with treatment failure. Female gender became more significantly associated with failed eradication (two-tailed, $P = 0.022$), while past medical history of peptic ulcer was not related to unsuccessful therapy (two-tailed, $P = 0.25$) (Table 2).

The reason for the apparent association between past medical history of peptic ulcer and treatment failure was that H_2RA pre-treatment was more likely to have been received in patients known to have peptic ulcer disease than in other dyspeptic patients. Thus, when past medical history of peptic ulcer and eradication failure were analyzed with H_2RA pre-treatment as a confounding factor the association was not significant (two-tailed, $P = 0.33$, Mantel Haenzel summary χ^2).

The effects of smoking and H_2RA pre-treatment on the efficacy of OCT were additive. *H. pylori* was eradicated in 95% (109/115) of non-smokers who had not received H_2RA pre-treatment, but was eradicated in only 81% (21/26) of those who had received H_2RA pre-treatment and in 87% (73/84) of smokers. *H. pylori* eradication was reduced to 68% (28/41) in patients with both risk factors. The effect of gender on the efficacy of OCT was independent of smoking or H_2RA pre-treatment status.

Discussion

Few studies have examined patient factors that predict failure of *H. pylori* eradication and, to our knowledge, this is the first report to undertake such an examination using the OCT regimen. We have shown that alcohol intake and past medical history of peptic ulcer did not affect the efficacy of OCT, these findings being in contrast with reports of previous studies using other *H. pylori* eradication regimens.[6,8] Labenz et al.[8] suggested that *H. pylori* eradication therapy was less effective in young patients, but other studies have not confirmed this,[6,10] and we could find no association between age and treatment failure. Diagnosis at endoscopy did not influence the efficacy of OCT in this study. A previous report has suggested that treatment was more effective in patients with gastric ulcer,[8] but we could not investigate this factor, as only 8 of the 273 patients (3%) in this study had a gastric ulcer at endoscopy. OCT was less effective in smokers, and such a finding has been reported previously with other *H. pylori* eradication regimens.[8,10] Suprisingly, OCT was also less effective in women and in those who had received H_2RA pre-treatment; these factors have not previously been associated with treatment failure.

Smoking has consistently been shown to be associated with *H. pylori* eradication failure. Compliance is an important determinant of treatment failure and smoking may simply be a marker of poor compliance. This, however, seems unlikely, because alcohol intake (also a marker of poor compliance) was not associated with treatment failure. Nitroimidazole resistance develops more readily in smokers,[11] but smoking also reduces the efficacy of regimens that do not contain this group of antibiotics.[8,10] It seems likely, therefore, that smoking has a direct effect in reducing the efficacy of *H. pylori* eradication regimens. Smoking increases acid output[12] and this could be one explanation. High intragastric acidity has been associated with treatment failure,[13] but this does not explain why larger doses of omeprazole do not improve eradication rates.[5] Smoking decreases gastric blood flow[14] and may inhibit treatment efficacy by reducing the delivery of antibiotic to the gastric mucosa. This theory is supported by the observation that it is the systemic concentration of antibiotic that predicts treatment success.[15]

H_2RA pre-treatment reduced the efficacy of OCT in this study. A previous study identified no relationship between the efficacy of dual omeprazole and amoxycillin therapy and H_2RA pre-treatment, but only 50 patients were investigated and the number of patients taking H_2RAs was not stated.[13] Omeprazole pre-treatment has been associated with failed eradication,[8] but this association may be due to confounding factors not controlled for in the study design. Although the intake of medication in our study was assessed by return tablet count and patient interview, this is a crude measure of compliance.[16] Patients who receive H_2RA or omeprazole pre-treatment may be less symptomatic than patients not taking these drugs and may be less likely to take antibiotics. This possibility can be discounted only by a prospective randomized double-blind placebo controlled trial. As OCT is an effective regimen, this type of study would require more than 500 patients, and would be impractical. It is possible that

pre-treatment with acid suppression directly affects efficacy. This is unlikely, however, because concomitant acid suppression enhances the efficacy of antibiotics.[17] H_2RAs and omeprazole reduce gastric blood flow[18,19] and might, thus, reduce the delivery of antibiotic to the gastric mucosa, although this is not a universal finding.[20] Smoking also reduces gastric mucosal blood flow; indeed, the effects of H_2RA pre-treatment and smoking on treatment failure were additive in this study. If this theory of reduced gastric blood flow is correct, then other factors that reduce gastric perfusion, such as NSAIDs,[21] should also reduce the efficacy of eradication therapy. The number of patients taking NSAIDs in this study was too small to investigate; however, another report has suggested that NSAID use was marginally associated with treatment failure.[13]

H. pylori could revert to a coccoid state after H_2RA pre-treatment. This phenomenon has been described after treatment with bismuth salts and may allow the organism to survive in a hostile environment.[22] In particular, coccoid *H. pylori* may be more resistant to antimicrobial therapy. In vitro studies would clarify whether H_2RA treatment can induce *H. pylori* to revert to the coccoid state.

When analyzed by multiple logistic regression, OCT was less effective in women. This is biologically plausible, as there are gender differences in gastric physiology;[23] however, this finding should be interpreted with caution. A large number of patients were investigated in this study, but due to the excellent eradication rates achieved with OCT there were few treatment failures. The small sample size of treatment failures could result in statistically significant associations being achieved by chance. Gender was not associated with treatment failure in another study using a different *H. pylori* eradication regimen.[12] Studies involving large numbers of patients are required to establish the role of gender in the efficacy of *H. pylori* eradication therapies.

This study suggests that OCT is less effective in women, smokers, and patients who have received H_2RA pre-treatment. These observations need further corroboration but, on the basis of these findings, it would be sensible, when possible, to avoid H_2RAs before OCT eradication therapy is commenced.

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References

1. Bazzoli F, Zagari RM, Fossi S, et al. Short-term low-dose triple therapy for the eradication of *Helicobacter pylori*. Eur J Gastroenterol 1994;6:773–777.
2. Goddard A, Logan R. One-week low-dose triple therapy: New standards for *Helicobacter pylori* treatment. Eur J Gastroenterol 1995;7:1–3.
3. Logan RPH, Gummett PA, Misiewicz JJ, et al. One-week eradication regimen for *Helicobacter pylori*. Lancet 1991;338:1249–1252.
4. Bell GD, Powell K, Burridge SM, et al. Experience with "triple" anti-*Helicobacter pylori* eradication therapy: Side effects and the importance of testing pre-treatment bacterial isolate for metronidazole resistance. Aliment Pharmacol Ther 1992;6:427–435.
5. Moayyedi P, Sahay P, Tompkins DS. Efficacy and optimum dose of omeprazole in new 1-week triple therapy regimen to eradicate *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1995;7:835–840.
6. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 1992;102:493–496.
7. Labenz J, Stolte M, Ruhl GH, Becker T, et al. One-week low-dose triple therapy for the eradication of *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 1995;7:9–11.
8. Labenz J, Leverkus F, Borsch G. Omeprazole plus amoxycillin for the cure of *Helicobacter pylori* infection—factors influencing the treatment success. Scand J Gastroenterol 1994;29:1070–1075.
9. Logan RPH, Dill S, Bauer E, et al. The European ^{13}C-urea breath test for the detection of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1991;3:915–921.
10. Unge P, Gad A, Eriksson K, et al. Amoxicillin added to omeprazole prevents relapse in the treatment of duodenal ulcer patients. Eur J Gastroenterol Hepatol 1993;5:325–331.
11. Witteman EM, Hopman WPM, Becx MCJM, et al. Short report: Smoking habits and the acquisition of metronidazole resistance in patients with *Helicobacter pylori*-related gastritis. Aliment Pharmacol Ther 1993;7:683–687.
12. Blair AJ, Feldman M, Barnett C, et al. Detailed comparison of basal and food-stimulated gastric acid secretion in normal subjects and patients with duodenal ulcer. J Clin Inv 1987;79:582–587.
13. Labenz J, Stolte M, Blum AL, et al. Intragastric acidity as a predictor of the success of *Helicobacter pylori* eradication: A study in peptic ulcer patients with omeprazole and amoxicillin. Gut 1995;37:39–43.
14. Holm L, Perry MA. Role of blood flow in gastric acid secretion. Am J Physiol 1988;G281–G293.
15. Adamek RJ, Wegener M, Labenz J, et al. Medium-term results of oral and intravenous omeprazole/amoxicillin *Helicobacter pylori* eradication therapy. Am J Gastroenterol 1994;89:39–42.
16. Pullar T, Kumar S, Tindall H. Time to stop counting tablets? Clin Pharmacol Ther 1989;46:163–168.
17. Axon ATR. The role of acid inhibition in the treatment of *Helicobacter pylori* infection. Scand J Gastroenterol 1994; 29(Suppl 201):16–23.
18. Varhaug JE, Svanes K, Lekven J. Regional gastric blood flow and acid secretion during histamine H_2-receptor blockade in cats. Scand J Gastroenterol 1983;18:977–986.
19. Holm-Rutili L. Effects of omeprazole on gastric micro-circulation in the rat. Gastroenterology 1987;92:716–723.
20. Polansky DB, Shirazi SS, Coon D. Lack of correlation of gastric acid secretion and blood flow. J Surg Res 1979;26:320–325.
21. Kauffman GL, Aures D, Grossman MI. Intravenous indomethacin and aspirin reduce basal gastric mucosal blood flow. Am J Physiol 1980;238:G131–G138.
22. Prewett EJ, Smith JTL, Nwokolo CU, et al. Twenty-four hour intragastric acidity and plasma gastrin concentration profiles in female and male subjects. Clin Sci 1991;80:619–624.
23. Bode G, Mauch F, Malfertheiner P. The coccoid forms of *Helicobacter pylori*. Criteria for their viability. Epidemiol Infect 1993;111:483–490.