

# The influence of pretreatment on cure rates of *Helicobacter pylori* eradication

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## ABSTRACT

**Background:** Many patients treated for *H. pylori* infection have been taking a proton pump inhibitor beforehand. There is conflicting evidence whether pretreatment influences the efficacy of *H. pylori* eradication. The aim of this study was to investigate the influence of pretreatment on cure rates of *H. pylori* eradication.

**Methods:** Patients with *H. pylori* positive peptic ulcer disease or functional dyspepsia were treated with two-day quadruple therapy (lansoprazole 30 mg twice daily, and colloidal bismuth subcitrate 120 mg, tetracycline 250 mg and metronidazole 250 mg, all eight times a day). Patients were randomised to receive either three-day pretreatment with lansoprazole 30 mg twice daily or no pretreatment. *H. pylori* was diagnosed using CLO, histology and culture.

**Results:** Twenty-five (66%) of 38 patients with pretreatment and 32 (84%) of 38 patients without pretreatment were cured ( $p=0.06$ ). After adjustment for diagnosis, smoking status and metronidazole resistance the influence of pretreatment became slightly less pronounced (OR 0.44, 95% CI 0.1-1.7). Nonsmokers and patients with peptic ulcer disease were more likely to achieve *H. pylori* eradication than smokers and patients with functional dyspepsia, respectively (adjusted odds ratios: 4.79 (1.2-19) and 4.32 (1.0-18)).

**Conclusions:** This two-day quadruple therapy reached an overall cure rate of 75%. Nonsmokers and patients with peptic ulcer disease were more likely to achieve *H. pylori* eradication. Three-day pretreatment with a proton pump inhibitor may decrease cure rates of this two-day quadruple therapy.

## INTRODUCTION

During the past decade it has been established that not only patients with peptic ulcer disease but also a subgroup of patients with functional dyspepsia benefit from *Helicobacter pylori* eradication.<sup>1,2</sup> Therefore *H. pylori* test-and-eradication has been incorporated in most guidelines for treatment of patients with dyspeptic symptoms.<sup>3</sup> As a result, many patients now receive therapy for *H. pylori* infection. Triple and quadruple therapies are usually used and achieve high cure rates<sup>4</sup> but none of the current therapies have reached a 100% cure in clinical trials<sup>5</sup> and several studies reported that cure rates in routine clinical practice are even lower.<sup>6</sup> Cure rates are influenced by antibiotic resistance,<sup>7</sup> duration of therapy<sup>8</sup> and compliance.<sup>9</sup> Another factor that has been implicated in therapy failure is pretreatment with a proton pump inhibitor. This may be an important factor as many patients treated for *H. pylori* infection are already on proton pump inhibitors.<sup>10</sup> Although pretreatment was advocated in the assumption that elevating gastric pH before starting the antibiotics would increase cure rates, several studies showed that pretreatment was related to therapy failure for dual therapy with omeprazole and amoxicillin. Eradication rates were 30 to 70% lower in patients with pretreatment.<sup>11-14</sup> The few studies investigating the influence of pretreatment on triple and quadruple therapies did not find differences in eradication rates for patients with and without pretreatment.<sup>15-17</sup> However, the high eradication rates of seven-day triple and quadruple therapies make it difficult to study factors associated with therapy failure. In this paper we used a very short quadruple therapy to study the influence of pretreatment. In our area, fairly high cure rates were reached with this quadruple regimen, and

because of its short duration we assumed it to be more vulnerable to the effect of pretreatment. That renders this regimen suitable for studying the effect of pretreatment in a fairly small population. The aim of this study was to evaluate the influence of three-day pretreatment with lansoprazole on cure rates of a two-day, intensified quadruple therapy, combining lansoprazole, bismuth, metronidazole and tetracycline.

## MATERIALS AND METHODS

### Study population

The study was conducted at Bernhoven Hospital, the Netherlands, in 1997, with approval of the local ethics committee. Patients over 18 years with *H. pylori* positive peptic ulcer disease or functional dyspepsia were eligible. Exclusion criteria were use of bismuth compounds/antibiotics/proton pump inhibitors during the past four weeks, prior *H. pylori* eradication, pregnancy or lactation and known allergic reaction to the study medication. All participating patients gave written informed consent.

### Investigations

All patients underwent upper gastrointestinal endoscopy both before and four to six weeks after treatment. At endoscopy seven biopsies were taken: four from the antrum (two for histology, one for CLO<sup>®</sup> (Delta West, Australia), one for culture) and three from the corpus (two for histology and one for CLO<sup>®</sup>). Biopsies for histological examination were fixed in neutral buffered 4% formaldehyde and *H. pylori* identification was performed on Giemsa-stained sections of paraffin embedded tissue. For culture Belo-Horizonte medium was used and plates were incubated microaerobically for seven days. Resistance to metronidazole and clarithromycin was determined by E-test<sup>®</sup> (AB Biodisk, Sweden) with cut-off values of 2 and 8 µg/ml, respectively. Patients were considered *H. pylori* positive when two out of three tests (CLO<sup>®</sup>, histology, culture) were positive. Patients were regarded to be cured when all three tests were negative.

Patient compliance was assessed both by interview and pill count. Side effects were registered using the questionnaire developed by De Boer *et al.*<sup>18</sup>

### Intervention

Patients received open-label therapy with two-day quadruple therapy consisting of lansoprazole 30 mg twice daily, together with colloidal bismuth subcitrate (De-Nol<sup>®</sup>) 120 mg, tetracycline 250 mg and metronidazole 250 mg (all taken eight times a day, at 9, 11, 13, 15, 17, 19, 21, and 23 hours). Patients were randomly allocated to three-day pretreatment with lansoprazole 30 mg twice daily or no pretreatment at all.

### Randomisation procedure

After inclusion each patient received a (sequentially) numbered, sealed, opaque, envelope containing the prescription (with or without pretreatment according to randomisation) and instructions on how to take the drugs. The envelopes were filled before the start of the study using a computer-generated randomisation list.

### Data analysis

Primary outcome of the study was *H. pylori* eradication. The study was designed as a pilot study with 80% power to detect a 20% decrease in cure rate due to pretreatment, for an estimated 85% cure rate of this quadruple therapy without pretreatment ( $\alpha=0.05$ ).

Baseline characteristics and eradication rates for both groups were compared using the  $\chi^2$  test. Pretreatment and baseline characteristics were related to *H. pylori* eradication by means of unadjusted and adjusted logistic regression analyses, using the SAS<sup>®</sup> statistical software package (SAS Institute Inc., USA). Statistical significance was defined as a  $p<0.05$ . Missing values were excluded from analyses.

## RESULTS

### Study population

Altogether, 76 patients were randomised. *Table 1* shows the baseline characteristics of these patients. Unfortunately, despite adequate randomisation, the pretreatment group contained more patients with functional dyspepsia.

**Table 1**

*Baseline characteristics (intention-to-treat population)*

	WITH PRETREATMENT (N=38)	WITHOUT PRETREATMENT (N=38)
<b>GENDER</b>		
Male	21 (55%)	29 (76%)
Female	17 (45%)	9 (24%)
<b>AGE</b>		
≤50 years	17 (45%)	14 (37%)
>50 years	21 (55%)	24 (63%)
<b>DIAGNOSIS (p&lt;0.05)</b>		
Peptic ulcer disease	14 (37%)	23 (61%)
Functional dyspepsia	24 (63%)	15 (39%)
<b>CURRENT SMOKING</b>		
	15 (39%)	19 (50%)
<b>ANTIBIOTIC SUSCEPTIBILITY</b>		
Metronidazole resistant	7 (23%)	5 (19%)
Metronidazole susceptible	24 (77%)	22 (81%)
Clarithromycin resistant	0 (0%)	0 (0%)
Clarithromycin susceptible	31 (100%)	27 (100%)

### Eradication rates, compliance and adverse events

Of 38 patients with pretreatment, 25 (66%) were cured, whereas 32 (84%) of 38 patients without pretreatment were cured ( $p=0.06$ ). All patients reported to have taken more than 90% of their pills.

The questionnaire on side effects was returned by 67 patients. Eighty-five percent of patients reported 'no side effects', or 'slight discomfort, not interfering with daily activities', 10% reported 'moderate side effects, sometimes interfering with daily activities' and 4% reported 'severe side effects'. None of the patients discontinued therapy because of side effects. Most frequently reported side effects were metallic taste, nausea and diarrhoea. There were no differences in incidence or severity of side effects between the treatment arms.

### Factors associated with treatment outcome

Table 2 shows that there is a tendency towards treatment failure for patients with pretreatment. For these patients the risk of treatment failure almost triples, although this effect becomes somewhat less pronounced after adjustment for diagnosis, smoking and metronidazole resistance. Furthermore, table 2 shows that diagnosis and smoking status are important predictors of treatment outcome. After adjustment, patients with peptic ulcer disease have an over four times greater chance of treatment success compared with patients with functional dyspepsia, whereas smokers have an almost five times greater chance of treatment failure compared with nonsmokers.

## DISCUSSION

The aim of this study was to investigate the influence of pretreatment with a proton pump inhibitor on *H. pylori* eradication. Many patients treated for *H. pylori* infection receive pretreatment, either intentionally, in an attempt to

enhance cure rates of *H. pylori* eradication as used to be advocated, or unintentionally, by using a proton pump inhibitor for treatment of gastrointestinal symptoms, peptic ulcer disease or reflux oesophagitis before starting *H. pylori* eradication. This warrants the need to further investigate the influence of pretreatment.

Theoretically, pretreatment with a proton pump inhibitor may influence eradication rates in several ways. Firstly, proton pump inhibitor therapy prevents degradation of acid labile antibiotics and decreases the minimum inhibitory concentration of the antibiotics.<sup>19</sup>

Consequently, pretreatment may increase the effectiveness of the first doses of antibiotics by elevating gastric pH before starting eradication therapy. Secondly, proton pump inhibitor therapy decreases bacterial load, especially in the antrum.<sup>20</sup> This may seem an advantage because less bacteria have to be killed. However, the remaining bacteria are in a less active, dormant, state<sup>21</sup> and are therefore less vulnerable to the actions of antibiotics.

In the present pilot study we evaluated the effect of three-day pretreatment with lansoprazole on eradication rates of a two-day intensified quadruple therapy. The results show a trend for patients with pretreatment towards lower eradication rates. But, although patients with pretreatment have an 18% lower cure rate, this difference does not reach statistical significance ( $p=0.06$ ). This may be due to type II error, as the power of this pilot study was only sufficient for detection of a difference of over 20%. Furthermore, adjustment for diagnosis, smoking status and metronidazole resistance slightly decreased the influence of pretreatment. This may be explained by the higher number of patients with functional dyspepsia, who have lower cure rates than patients with peptic ulcer disease, in the pretreatment group.

However, a 10 to 20% decrease may well be possible with

Table 2

Factors associated with treatment outcome

FACTOR	UNADJUSTED ANALYSIS			ADJUSTED ANALYSIS*		
	ODDS RATIO	95% CI	P VALUE	ODDS RATIO	95% CI	P VALUE
Pretreatment (vs no pretreatment)	0.36	0.1-1.1	0.06	0.44	0.1-1.7	0.23
Diagnosis (peptic ulcer disease vs functional dyspepsia)	2.58	0.9-7.8	0.09	4.32	1.0-18	0.05
Smoking (vs no smoking)	0.37	0.1-1.1	0.06	0.21	0.1-0.8	0.03
Metronidazole resistance (resistant vs susceptible)	0.44	0.1-1.7	0.22	0.51	0.1-2.3	0.39
Gender (male vs female)	1.58	0.5-4.6	0.40			
Age class (>50 years vs ≤50 years)	1.08	0.4-3.1	0.89			

\* Adjusted for pretreatment, diagnosis, smoking and metronidazole resistance.

this two-day quadruple therapy. An effect of that magnitude would be clinically relevant and might have consequences for clinical practice. Possibly, patients on a proton pump inhibitor should be advised to either interrupt the proton pump inhibitor therapy before starting *H. pylori* eradication or take an eradication regimen of longer duration.

We used a two-day quadruple therapy in order to be able to demonstrate the influence of pretreatment without the necessity to study a large number of patients. Seven-day quadruple regimens have higher cure rates and may possibly overcome any deleterious effect of pretreatment. However, there are no published data on this. For seven-day proton pump inhibitor triple therapy, two studies investigating 89 and 101 patients found no difference in cure rates between patients with and without pretreatment.<sup>16,17</sup> However, the high cure rates of these therapies require large study populations to detect a 10 to 15% difference in eradication rates. Therefore more research is necessary to definitely settle the issue of pretreatment.

The overall eradication rate of this two-day quadruple therapy was 75%, which is comparable with other research with two-day quadruple therapy.<sup>22,23</sup> Although this is inadequate for use in routine clinical practice, these results after just two days of therapy emphasise the efficacy of quadruple therapy.

Being a nonsmoker and having peptic ulcer disease were associated with a greater chance of achieving *H. pylori* eradication. Smoking has been identified by several studies to be an important factor associated with treatment failure.<sup>24-26</sup> The underlying mechanism is still unknown, although decreased gastric blood flow,<sup>27</sup> damage to the gastric mucosa,<sup>28</sup> and increased acid secretion<sup>29</sup> have been implicated.

The higher cure rates for patients with peptic ulcer disease (vs functional dyspepsia) are consistent with other studies, typically reporting 5 to 15% higher eradication rates for patients with peptic ulcer disease.<sup>30-32</sup> This may be caused by the higher prevalence of more virulent *H. pylori* strains<sup>33,34</sup> which cause more inflammation<sup>35</sup> in patients with peptic ulcer disease, as several studies have shown that patients with more virulent strains<sup>36</sup> and with more inflammation<sup>37</sup> can be cured more easily.

In conclusion, this two-day quadruple therapy reached an overall cure rate of 75%. Although this is not sufficient for use in routine clinical practice, these results after just two days of therapy emphasise the potency of quadruple therapy in general. Nonsmokers and patients with peptic ulcer disease were more likely to achieve *H. pylori* eradication. Three-day pretreatment with a proton pump inhibitor may decrease cure rates of two-day quadruple therapy, but more research is necessary to definitely establish the influence of pretreatment with a proton pump inhibitor on routine therapy for *H. pylori* eradication.

## NOTE

The authors received no funding for this study. There were no conflicts of interest.

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