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Comparison of four-day and seven-day pantoprazole-based quadruple therapy as a routine treatment for *Helicobacter pylori* infection

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ABSTRACT

Background: *H. pylori* eradication is usually performed with three or four drugs for at least seven days. Recently four reports have shown a cure rate of approximately 90% using a four-day quadruple therapy. The objectives of this prospective study were: 1) to evaluate the efficacy of pantoprazole-based quadruple therapy, and 2) to compare the efficacy and tolerability of four-day with seven-day quadruple therapy.

Methods: The study was performed in a single centre. The first 56 consecutive patients with nonulcer dyspepsia or peptic ulcer disease and proven *H. pylori* infection received seven days of quadruple therapy (pantoprazole, bismuth, tetracycline and metronidazole). At least six weeks after treatment, endoscopy was repeated with six biopsies of the antrum and corpus for histology, urease test and culture. The next 59 consecutive patients followed the same protocol but received four-day quadruple therapy.

Results: Using an intention-to-treat analysis, the cure rate in the seven-day treatment group was 54/56 (96.4%, 95% confidence interval (CI) 87.7-99.6%). In the per protocol analysis the cure rate was 53/55 (96.3%, 95% CI 87.5-99.6%). Primary metronidazole resistance was observed in seven patients. All were cured. Using an intention-to-treat analysis, the cure rate in the four-day treatment group was 51/59 (86.4%, 95% CI 75.0-94.0%). In the per protocol analysis the cure rate was 50/58 (86.2%, 95% CI 74.6-93.8%). Primary metronidazole resistance was observed in seven patients, four of whom were cured. In three out of eight patients in whom four-day treatment failed, secondary metronidazole resistance was induced. Both treatment regimens were well tolerated. The difference between cure rates of both regimens did not reach statistical significance (p=0.0585).

Conclusion: Routine use of both four-day and seven-day pantoprazole-based quadruple anti-*H. pylori* treatment is effective and well tolerated. The results of both regimens reach the required eradication standard, but results with the seven-day regimen were slightly but not significantly better. Seven-day treatment may be superior, especially in case of metronidazole resistance, and should be preferred.

INTRODUCTION

Curing *Helicobacter pylori* infection has become the standard treatment for patients with *Helicobacter*-associated peptic ulcer disease.[1] Antibiotic treatment, however, is still not standardised and a variety of treatment schedules are used. Most regimens consist of three or four drugs, usually administered for between seven to 14 days. The success rate of a given treatment depends on the potency of its components and their dosing schedule, but also on other factors such as antibiotic resistance of *H. pylori*, the infective strain and patient compliance, which is partly determined by the occurrence of adverse effects.[2,3]
To achieve a simpler treatment with less adverse effects and better patient compliance, shortening the duration of treatment has been proposed.[4-8] Adding a proton pump inhibitor (PPI) to bismuth triple therapy (quadruple therapy) improves the cure rate.[9] Although this is probably a class effect of the PPIs, pantoprazole has not yet been used in

a quadruple regimen. Recently, four papers reported the results of a four-day quadruple treatment with omeprazole and lansoprazole.[5-8] The results of these studies showed a cure rate of approximately 90% and therefore four-day quadruple treatment may be attractive.
To compare the results of a seven-day with a four-day treatment in a single centre, we conducted a prospective, open, nonrandomised study testing the efficacy and adverse effect profile of first a seven-day and then a four-day pantoprazole-based quadruple therapy. In contrast to the previous four-day lansoprazole- or omeprazole-based quadruple treatment studies, in the present study pantoprazole was used in the quadruple regimen.

PATIENTS AND METHODS

The patients who participated in this study were consecutive outpatients referred for gastrointestinal investigation to Slingeland Hospital, Doetinchem, the Netherlands. This is a nonacademic community hospital situated in a rural area in the east of the Netherlands. Patients with nonulcer dyspepsia as well as patients with proven ulcer disease in whom endoscopic biopsies had confirmed the presence of *H. pylori* and in whom antibiotic therapy was indicated participated in this study. Before entering the study, patients were informed about the study design and gave their oral informed consent. The study protocol was not submitted to the Medical Ethics Committee of Slingeland Hospital, since the authors felt that four-day as well as seven-day quadruple treatment were standard and accepted anti-*Helicobacter* treatment schedules.

H. pylori status

Before inclusion and at least six weeks after cessation of treatment, *H. pylori* infection was proven with endoscopy. Six biopsies were taken. First, a antral biopsy was taken for a rapid urease test prepared by the hospital pharmacist.[10] Then, a antral biopsy was taken for culture with an antibiogram for metronidazole and clarithromycin by means of an agar dilution method. Metronidazole resistance was defined as a mean inhibitory concentration (MIC) value >8 μg/ml and clarithromycin resistance was defined as a MIC value >2 μg/ml. Finally two biopsies from the antrum and two from the corpus were taken for histology using a modified Giemsa stain. At the pretrial endoscopy 115 patients were biopsied according to the protocol. In five patients no *H. pylori* culture was performed. At the post-trial endoscopy a patient was only considered to be cured if all biopsy-based tests were negative for the presence of *H. pylori*. Pretreatment use of PPIs, defined as the use of a PPI for three or more days prior to the first endoscopy and the start of the anti-*H. pylori* treatment, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) were recorded in all patients.

Treatment

The first consecutive 56 patients were treated with seven-day quadruple therapy to judge the efficacy of pantoprazole-based quadruple therapy. The next 59 consecutive patients were treated with four-day quadruple therapy. Patients were prescribed the following treatment for seven or four days: pantoprazole (Pantozol, Altana Pharma, Zwanenburg, the Netherlands) 40 mg bd before breakfast and before the evening meal, bismuth (tripotassium dicitrato bismuthate, De-Nol, Yamanouchi Pharma, Leiderdorp, the Netherlands) 120 mg qid before the three meals and at bedtime, tetracycline hydrochloride 500 mg qid with the three meals and at bedtime, and metronidazole 500 mg tid with the three meals. In both regimens, pretreatment with a PPI was not obligatory. Patients received the medication from their own pharmacies. The use of alcohol was discouraged. Patients were instructed to take their treatment precisely as prescribed. They were informed about possible adverse effects.

Tolerability

Tolerability and adverse effects were assessed with an internationally accepted questionnaire in which patients were asked to judge these aspects of the treatment on a scale of A to E: category A was no adverse effects, category B slight discomfort not interfering with daily activities, category C moderate adverse effects interfering with daily activities, category D severe adverse effects, work not possible, and category E severe adverse effects, discontinuation of treatment.[11]

Compliance

Compliance was assessed by counting the medication returned within one week after the medication had been taken.

Statistical analysis

Statistical analysis was performed with a Mann-Whitney U-Wilcoxon rank-sum W test. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of 115 consecutive patients (61 male, 54 female) were included between July 1997 and March 1998. Mean age was 56 years (range 22 to 87 years). Indications for treatment were nonulcer dyspepsia (n=67, 58%), gastric ulcer disease (n=9, 8%), erosive bulbitis, or first or recurrent duodenal ulcer disease (n=39, 34%). Of the 115 patients, 18 were immigrants. Characteristics of both treatment groups are shown in *table 1*.
Follow-up was available for all patients. In the seven-day treatment group, using intention-to-treat, 54 out of 56

Table 1
Patient characteristics

	SEVEN-DAY TREATMENT (N=56)	FOUR-DAY TREATMENT (N=59)
Males/females	26/30	35/24
Age (years)	57.7 (23-87)	55.9 (22-77)
Immigrants	10 (18%)	8 (14%) n.s.
Diagnosis		
Nonulcer dyspepsia	32 (57%)	35 (59%) n.s.
Gastric ulcer	5 (9%)	4 (7%) n.s.
Duodenal ulcer	19 (34%)	20 (34%) n.s.
NSAID users	13 (23%)	10 (17%) n.s.
PPI pretreatment	15 (27%)	24 (41%) n.s.

patients (96.4%, 95% CI 87.7-99.6%) were negative for *H. pylori* after treatment. In the per protocol analysis, the cure rate was 53/55 (96.3%, 95% CI 87.5-99.6%). In three patients the results of the rapid urease test were lost. Before treatment, results of metronidazole and clarithromycin susceptibility testing were available in 40 patients. One patient (2.5%) carried a clarithromycin-resistant strain. Seven (17.5%) carried a metronidazole-resistant strain. They were all cured. No metronidazole resistance was induced in the two patients who were not cured (also see *table 2*). In the four-day group, intention-to-treat cure levels were 51 out of 59 (86.4%, 95% CI 75.0-94.0%). In the per protocol analysis the cure rate was 50 out of 58 (86.2%, 95% CI 74.6-93.8%). One patient refused a second endoscopy and post-treatment *Helicobacter* status was obtained with a carbon-13 breath test. Results of primary metronidazole susceptibility testing were available in 53 patients. Seven of these patients (13%) carried a metronidazole-resistant strain. Four of these patients were cured. In three patients in whom therapy failed, secondary metronidazole resistance was found post-treatment (see also *table 2*). Of the eight treatment failures in the four-day treatment group, four patients were not pretreated with a PPI immediately before starting the anti-*Helicobacter* treatment. The cure rates, intention-to-treat and per protocol were not significantly different between the four- and seven-day regimens (p=0.0585), but there was a trend towards higher efficacy in the seven-day group, especially in patients with a metronidazole-resistant strain.

Table 2
Cure rates and adverse effects

	SEVEN-DAY TREATMENT (N=56)	FOUR-DAY TREATMENT (N=59)
Cure rate		
Intention to treat	54/56 (96.4%)	51/59 (86.4%) n.s.
Per protocol	53/55 (96.3%)	50/58 (86.2%) n.s.
Metronidazole resistance	7/40 (17%)	7/51 (13%) n.s.
Immigrants	2/10 (20%)	1/8 (13%) n.s.
Cure rate metronidazole		
Sensitive strains	32/33 (97%)	42/46 (91%) n.s.
Resistant strains	7/7 (100%)	4/7 (57%) n.s.
Cure rate		
No PPI pretreatment	40/41 (98%)	31/35 (89%) n.s.
PPI pretreatment	14/15 (93%)	20/24 (83%) n.s.
Cure rate		
Immigrants	10/10 (100%)	7/8 (88%) n.s.
Residents	44/46 (96%)	44/51 (86%) n.s.
Metronidazole resistance induced	0/2 (0%)	3/8 (37%) n.s.
Adverse effects		
A (no discomfort)	9 (16%)	21 (35%)
B (light discomfort)	33 (59%)	23 (39%)
C (moderate side effects)	11 (20%)	11 (18%)
D (severe side effects)	2 (4%)	4 (7%)
E (discontinuation)	1 (2%)	0 (0%)

Compliance and adverse effects
The compliance was excellent and there were no differences for patients receiving four-day *versus* seven-day treatment. Only one patient, who was in the seven-day treatment group, stopped taking the drugs after four days. The overall dropout rate was therefore less than 1%.
The reported adverse effects were mild. No serious adverse events were observed. The adverse effects that were reported, such as nausea, headache, diarrhoea and general malaise, were of short duration and in all except one patient were not a reason for stopping the treatment prematurely. We used a well-known questionnaire in which patients were asked to judge the tolerability of the treatment on a scale from A to E.[11] Of the patients, 29 (25%) chose category A, 66 (57%) category B, 22 (19%) category C, and 6 patients (5%) chose category D. One of the patients, the previously mentioned noncompliant patient, chose category E but in this patient the *Helicobacter pylori* infection was nevertheless eradicated (also see *table 2*). No significant differences were found in adverse effects between both treatment groups, when groups A and B, and groups C, D and E were taken together. No significant differences in adverse effects were found between the patients who were cured and those who were not.

DISCUSSION

It is generally accepted that the combination of a PPI, bismuth, tetracycline and metronidazole is a potent drug combination for the treatment of *H. pylori*, even in areas with a high incidence of metronidazole resistance.[9,12,13] Although we used this treatment as the first-line approach to this infection, others have suggested only using this regimen in patients in whom a previous regimen has failed.[14] The Maastricht 2000 European consensus advises starting with a PPI- or ranitidine-bismuth-subcitrate-based triple therapy, but to use quadruple therapy in the second

line for the failures of triple therapy.[15] The first goal of this study was to determine the effect of pantoprazole in combination with the classical triple therapy in the treatment of *H. pylori*. With a cure rate of more than 95% and no failures in seven patients with metronidazole-resistant strains, it seems that seven-day pantoprazole-based quadruple therapy is as effective as other seven-day PPI-based quadruple therapies.[4,9,13-22]

Since patient compliance, drug tolerability and adverse effects are major factors determining the success of treatment, shortening the treatment period has been tried in many studies to find an optimal balance between cure rate, adverse effects and the induction of antibiotic resistance against *H. pylori*. This allowed the exploration of treatments shorter than seven days. Two-day quadruple therapy was not sufficiently effective.[4,23] Recently four Dutch studies showed that a four-day quadruple therapy with either omeprazole or lansoprazole as a PPI was very effective and well tolerated.[5-8] In the present study we confirmed the findings of these four-day studies in a routine clinical setting. The cure rate (86%) was somewhat lower compared with the former studies (about 90%), but reaches the efficacy requirements put forward by the European *Helicobacter pylori* Study Group.[24] In patients infected with metronidazole-resistant strains the cure rate was suboptimal and lower than in patients with metronidazole-sensitive strains or those treated for seven days. Three of the eight patients in whom the four-day therapy failed developed secondary resistance against metronidazole. Induction of metronidazole resistance was not found in the previous four-day quadruple therapy studies, but the number of failures is low and the clinical significance of this finding is not clear.

Clinically relevant adverse effects did not differ between the regimens. The question can be raised whether the advantage of efficacy of about 10% in favour of the seven-day treatment group, together with the metronidazole-resistance induction found in the four-day treatment group, should be an argument to treat all patients for at least seven days. We have confirmed the high efficacy of seven-day therapy in the metronidazole-resistant strains, whereas with four days the results of previous studies have also shown a decrease in efficacy, mainly in the metronidazole-resistant strains.[5-8]

In this study most patients were not pretreated with a PPI before starting with the antibiotics. In the previous four-day quadruple studies, patients were always pretreated with a PPI three days before the treatment started, with the argument that PPI pretreatment should augment the treatment response.[9] There are, however, no firm data to show that this hypothesis is correct. Annibale *et al.* found no advantage of PPI pretreatment in the anti-*H. pylori* treatment in peptic ulcer patients.[25] In both our seven-day and four-day regimens the results were slightly, but not significantly, higher in the patients without PPI pretreatment (*table 2*). This study was not designed to study the role of pretreatment with acid inhibition, and firm conclusions cannot be drawn from this limited data.

We have demonstrated that both pantoprazole-based quadruple therapies are well tolerated and attractive for use in a routine setting to eradicate *H. pylori* in an area with relatively low metronidazole resistance. Only one patient had severe side effects, which led to discontinuation of treatment on the 4th day, but the *H. pylori* infection was nevertheless eradicated. In our hands, shortening of the treatment duration was not an instrument to improve compliance. The adverse effect profile is comparable with the findings of other authors.

Although we acknowledge the limitations of this non-randomised study, we feel that we have shown that the cure rates of the seven-day treatment group were, although not statistically significant, superior to the four-day treatment group especially in patients carrying a metronidazole-resistant strain. We have also shown that the adverse effects in both treatment groups were comparable. The authors feel that shortening of a seven-day quadruple treatment to four days carries a certain risk of lower cure rates, mainly in resistant strains, whereas we could not demonstrate any advantage of four-day therapy in terms of better compliance or adverse effect profile.

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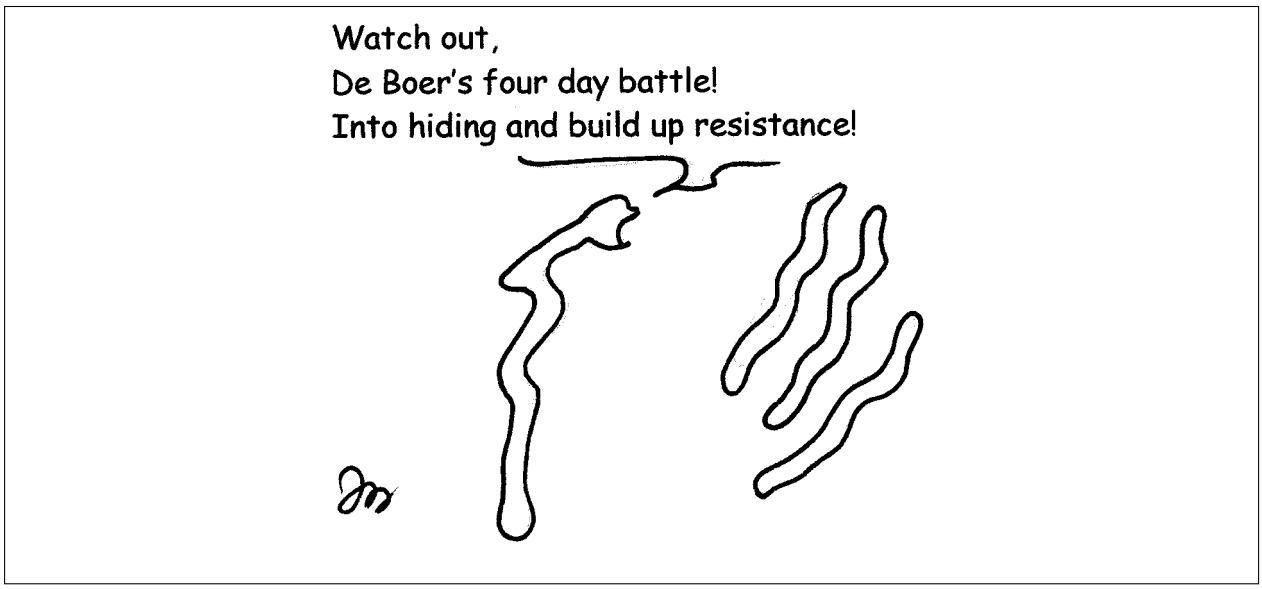
REFERENCES

1. Hopkins RJ, Girardi LS, Turney EA. Relationship between *H. pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996;110:1244-52.
2. Doorn LJ van, Schneeberger PM, Novhan N, Plaisier AP, Quint WGV, Boer WA de. Importance of *Helicobacter pylori* CAG-A and VAC-A status for the efficacy of antibiotic treatment. Gut 2000;46:321-6.
3. Houben MHMG, Beek D van de, Hensen EF, Craen ASM de, Rauws EAS, Tytgat GNS. A systematic review of *Helicobacter pylori* eradication therapy. The impact of antimicrobial resistance on eradication rates. Aliment Pharmacol Ther 1999;13:1047-55.
4. Kung NNS, Sung JJY, Yuen NWF, et al. Anti-*Helicobacter pylori* treatment in bleeding ulcers: randomised controlled trial comparing 2-day versus 7-day bismuth quadruple therapy. Am J Gastroenterol 1997;92:438-41.
5. Boer WA de, Driessen WWM, Tytgat GNJ. Only four days of quadruple therapy can effectively cure *Helicobacter pylori* infection. Aliment Pharmacol Ther 1995;9:633-8.
6. Boer WA de, Etten RJXM van, Schade RBW, Ouwehand ME, Scheeberger PM, Tytgat GNJ. 4-day lansoprazole quadruple therapy is very effective in curing *Helicobacter pylori* infection. Am J Gastroenterol 1996;91:1778-82.

7. Boer SY de, Siem TH. Four day quadruple therapy as a routine treatment for *Helicobacter pylori* infection. Aliment Pharmacol Ther 1997;11:1119-21.
8. Boer WA de, Etten RJXM van, Schneeberger PM. Four-day Lansoprazole-quadruple therapy in the routine treatment of *Helicobacter pylori* infection. Neth J Med 1998;52:10-5.
9. Boer WA de, Driessen WMM, Jansz AR, Tytgat GNJ. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. Lancet 1995;345:817-20.
10. Arvind AS, Cook RS, Tabaqchali S, Farthing MJG. One minute endoscopy room test for *Campylobacter pylori*. Lancet 1988;1/8587:704.
11. Boer WA de, Thys JC, Borody TJ, Graham DY, O'Morain C, Tytgat GNJ. Proposal for use of a standard side effect scoring system in studies exploring *H. pylori* treatment regimens. Eur J Gastroenterol Hepatol 1996;8:641-3.
12. O'Morain C, Borody A, Boer WA de, et al. Efficacy and safety of single triple capsules of bismuth citrate, metronidazole and tetracycline, given with omeprazole, for the eradication of *Helicobacter pylori*: an international multicentre study. Aliment Pharmacol Ther 2003;17:415-20.
13. Katelaris PH, Forbes GM, Talley NJ, Crotty B. A randomised comparison of quadruple and triple therapies for *Helicobacter pylori* eradication: the quadrate study. Gastroenterology 2002;123:1763-9.
14. Boer WA de. Strategies for therapy failures: choice of 'back-up' regimen determined by primary treatment for *Helicobacter pylori* infection. In: Hunt RH, Tytgat GNS (eds). *Helicobacter pylori* basic mechanisms to clinical cure 2000. Dordrecht: Kluwer Academic Publishers, 2000:609-22.
15. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection. The Maastricht 2-2000 Consensus report. Aliment Pharmacol Ther 2002;16:167-80.
16. Chan FKL, Yung MY, Ling TKW, Leung WK, Chung SCS. What is the true impact of metronidazole resistance on the efficacy of bismuth triple therapy? Gut 1998;43(suppl 2):A85.
17. Borody TJ, Andrews P, Shortis NP, Hyland I. Seven day therapy for *Helicobacter pylori*. Gastroenterology 1995;108:A62.
18. Vautier G, Scott BB. A one week quadruple regimen for *Helicobacter pylori* in routine clinical practice. Aliment Pharmacol Ther 1997;1:107-8.
19. Boer WA de, Etten RJXM van, Lai JYL, Schneeberger PM, Wouw BAM van de, Driessen WMM. Effectiveness of quadruple therapy using lansoprazole instead of omeprazole in curing *Helicobacter pylori* infection. Helicobacter 1996;1:145-50.
20. Gomollon F, Gimeno L, Valdeperez S, Yus J, Marzo J, Perez-Caballero. Eradication of *Helicobacter pylori* among patients from a primary care practice. J Fam Pract 1996;43:551-5.
21. Lai Yjl, Grauw JC de, Boer WA de. *Helicobacter* treatment with quadruple therapy in primary health care for patients with a history of ulcer disease. Fam Pract 1999;16:483-8.
22. Borody TJ, Andrews P, Fraccuia G, Brandl S, Shortis NP, Bae H. Omeprazole enhances efficacy of triple therapy in eradicating *Helicobacter pylori*. Gut 1995;37:477-81.
23. Boer WA de, Etten RJXM van, Coremans A, Schneeberger PM. Two-day 'weekend' lansoprazole quadruple therapy for *Helicobacter pylori* infection. Aliment Pharmacol Ther 1998;12:77-81.
24. European Helicobacter Pylori Study Group. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht consensus report. Gut 1997;41:8-13.
25. Annibale B, D'Ambra G, Luzzi I, et al. Does pre-treatment with omeprazole decrease the chance of eradication of *Helicobacter pylori* in peptic ulcer patients. Am J Gastroenterol 1997;92:790-4.



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