

Seven-day PPI-triple therapy with levofloxacin is very effective for *Helicobacter pylori* eradication

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ABSTRACT

Background: *Helicobacter pylori* infection causes lifelong gastritis and is associated with the development of peptic ulcer disease, MALT lymphoma and gastric cancer. Many patients benefit from *H. pylori* eradication therapy. PPI-triple therapy is recommended as initial therapy. Quadruple therapy, with a PPI, bismuth, and two antibiotics, used to be recommended as second-line therapy, but can no longer be prescribed because bismuth is no longer available. Therefore, there is an urgent need for new effective rescue therapies. Levofloxacin-based therapies were suggested as an alternative to quadruple therapy. The aim of this study is to examine the efficacy and tolerability of such a one-week therapy with levofloxacin and esomeprazole combined with either amoxicillin or clarithromycin in a Dutch population.

Methods: Between February 2005 and November 2006, 123 consecutive *H. pylori* positive patients were enrolled in this study. The first 59 patients were treated with esomeprazole, amoxicillin and levofloxacin (group I). The next 64 patients were treated with esomeprazole, clarithromycin, and levofloxacin (group II). Both therapies were compared for efficacy and tolerability.

Results: In group I the overall (ITT) cure rate was 96% and in group II it was 93%. Minor side effects occurred in 29% of patients in group I and in 41% of patients in group II. Major side effects that warranted discontinuation of therapy occurred in two patients in group II.

Conclusion: Seven-day triple therapy with esomeprazole, levofloxacin and either amoxicillin or clarithromycin for seven days is very effective and safe for *H. pylori* eradication. The combination with amoxicillin seems to be better tolerated than the combination with clarithromycin.

KEYWORDS

Helicobacter pylori, levofloxacin, therapy

INTRODUCTION

Helicobacter pylori infection causes life-long gastritis and is associated with the development of peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.¹ Some dyspeptic patients and even asymptomatic persons benefit from *H. pylori* eradication therapy. Most experts believe that eradication of *H. pylori* may possibly prevent gastric cancer.^{2,3} There are several well-investigated eradication therapies available. The ideal therapy for this common infection should be simple, safe, cheap, well-tolerated and of short duration, and above all it should reach a high cure rate.

Most guidelines, including the Dutch Institute for Healthcare Improvement (CBO)/Dutch College of General Practitioners (NHG) guideline 'Gastric complaints',⁴ advise triple therapy with a proton pump inhibitor (PPI) and two different antibiotics for an initial attempt at *H. pylori* eradication. After a first antibiotic treatment, a urea breath test to test for cure is usually recommended. In case of persisting infection, the guidelines recommend the use of quadruple therapy, which contains a PPI, bismuth subcitrate and two different antibiotics.⁵⁻¹¹ Although this therapy has the disadvantage of a complicated dosing regimen, it is very effective and is even considered to be a first-line treatment in some countries.

However, unfortunately, in the Netherlands and many other European countries, bismuth is no longer available and quadruple therapy can therefore no longer be prescribed. A possible solution could be the use of a new single multi-drug anti-*Helicobacter* capsule that contains bismuth, tetracycline and metronidazole, but even though this drug has now been approved by the FDA it has not yet received approval from the European authorities to enter the market.¹² Hence, there is an urgent need for new effective therapies in the Netherlands, especially for backup after failure of a first-line PPI-triple therapy.

Levofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against both Gram-positive

and Gram-negative bacteria as well as atypical respiratory pathogens.¹³ Several studies demonstrated the efficacy of levofloxacin in the treatment of infection of the respiratory tract, genitourinary tract, skin and skin structures.¹³ The antibacterial activity coupled with its excellent bioavailability and ease of dosing make levofloxacin an attractive antibiotic for treatment of *H. pylori* infection. Recently, some studies have reported excellent results with the use of levofloxacin in *H. pylori* eradication, not only as first-line therapy but also as second line and as rescue therapy.¹⁴⁻²⁹ In association with other antibiotics, levofloxacin reached high *H. pylori* eradication rates (often over 90%) with a low incidence of side effects. All eradication studies with levofloxacin were performed in other countries than the Netherlands and these data need confirmation in our country.^{30,31} Therefore, the aim of the present study is to examine the efficacy and tolerability of a one-week therapy with levofloxacin, esomeprazole and either amoxicillin or clarithromycin in a Dutch population.

PATIENTS AND METHODS

Between February 2005 and November 2006, 123 consecutive *H. pylori* positive patients who visited Bernhoven Hospital (Oss) due to dyspepsia, with or without ulcer disease, were enrolled in this open-label study. Bernhoven Hospital is a non-academic community hospital in the southeast of the Netherlands. In all patients, *H. pylori* status was determined by analysis of gastric biopsies or through a well-validated ¹³C urea breath test (BreathID™, Oridion Systems).³² The first 59 patients were treated with esomeprazole 40 mg (Nexium®), amoxicillin 1000 mg and levofloxacin 500 mg (Tavanic®), all given twice daily for seven days (Group I). The next 64 patients were treated with esomeprazole 40 mg (Nexium®), clarithromycin 500 mg, and levofloxacin 500 mg (Tavanic®), all given twice daily for seven days (Group II). Patients were instructed to take their treatment precisely as prescribed and were informed about possible side effects. Furthermore, patients were asked whether they had undergone previous attempts to eradicate *H. pylori* or whether they had received pretreatment with a PPI. At least five weeks after finishing therapy, *H. pylori* status was tested again with either biopsy-based tests if endoscopy was clinically indicated or otherwise with the ¹³C urea breath test. Side effects were recorded by the treating physician at the end of the treatment and graded on a five-point, internationally accepted scale, which we have described before. This scale contains five categories, ranging from 'no adverse effects' (category A), 'slight discomfort not interfering with daily activities' (category B), 'moderate adverse effects interfering with

daily activities' (category C), 'severe adverse effects, work not possible' (category D), to 'severe adverse effects, discontinuation of treatment' (category E).³³ The two therapies were compared for efficacy and tolerability.

Upper gastrointestinal endoscopy

A subgroup of patients underwent upper gastrointestinal endoscopy. During endoscopy seven biopsies were taken. Four (2 antrum and 2 corpus) for histology, two (1 antrum and 1 corpus) for two separate CLO-tests® and one (1 antrum) for culture. Patients were considered *H. pylori* positive if one of these three different tests on either antrum or corpus biopsies was positive.

¹³Urea breath test

Another subgroup of patients had a *H. pylori* urea breath test (BreathID™ from Oridion Systems, a commercially available and well-validated near-patient ¹³C-urea breath test), instead of endoscopy.³² Care was taken to ensure that patients had not taken any PPIs for at least one week before the urea breath test. Breath samples were recorded as positive if the ¹³CO₂/¹²CO₂ ratio was above 5‰. Values below the 5‰ cut-off were considered to be *H. pylori* negative. This test provides excellent sensitivity and specificity in diagnosing *H. pylori* infection, both before and after *H. pylori* eradication.

Statistical analysis

Baseline characteristics of both patient groups were compared using the Student's t-test or χ^2 square test where appropriate. *H. pylori* eradication rates with 95% confidence intervals were calculated and compared using the χ^2 test. This analysis was repeated for the subgroup of patients with a prior (failed) attempt to eradicate *H. pylori*. For analyses the SAS® statistical software package (SAS Institute Inc., USA) was used. Statistical significance was defined as a p value <0.05. Missing values were excluded from analyses.

RESULTS

Population

A total of 123 consecutive *H. pylori* positive patients (mean age 53 (SD 16), 44% male,) were included between February 2005 and November 2006. Twenty-seven of these patients had a diagnosis of peptic ulcer disease (22%). The first 59 patients were treated with esomeprazole, amoxicillin and levofloxacin (group I), the following 64 patients with esomeprazole, clarithromycin and levofloxacin (group II). Table 1 shows that, although not randomised, both patient groups had similar baseline characteristics. However, there were more patients with a history of failed *H. pylori* eradication in group I.

Table 1. Baseline characteristics

	Levofloxacin, esomeprazole and amoxicillin (n=59)	Levofloxacin, esomeprazole and clarithromycin (n=64)	P value for difference
Mean age	55 years (SD 15)	52 years (SD 16)	0.26
Male gender	26 (44%)	28 (44%)	0.97
Smoking	17 (29%)	20 (31%)	0.77
PPI-pretreatment	18 (31%)	23 (36%)	0.53
Previous therapy failure	14 (24%)	5 (8%)	0.01
Body mass index	25.7 (SD 3.9)	26.1 (SD 4.5)	0.62

PPI = proton pump inhibitor.

Table 2. Effectiveness of *Helicobacter pylori* eradication

	Levofloxacin, esomeprazole and amoxicillin (n=59)	Levofloxacin, esomeprazole and clarithromycin (n=64)	P value for difference
<i>Helicobacter pylori</i> eradicated (ITT)	57 (97%)	59 (92%)	0.29
<i>Helicobacter pylori</i> eradicated (PP)	57 (97%)	59 (95%)	0.69
Side effects	17 (29%)	26 (41%)	0.17
Cessation due to side effects	0 (0%)	2 (3%)	0.17
2nd/3rd line therapy (ITT)	14/14 (100%)	4/5 (80%)	0.09
First-line therapy (ITT)	43/45 (96%)	55/59 (93%)	0.61

ITT = intention to treat; PP = per protocol.

Effectiveness of *H. pylori* eradication

Of the 59 patients treated with esomeprazole, amoxicillin and levofloxacin, 57 were cured of their *H. pylori* infection, yielding a 97% cure rate (95% CI 92 to 100%), both for intention-to-treat (ITT) and per protocol (PP) analysis. Of the 64 patients treated with esomeprazole, clarithromycin and levofloxacin, 59 had successful *H. pylori* eradication, yielding an ITT cure rate of 92% (95% CI 86 to 99%) and a PP cure rate of 95% (95% CI 90 to 100%) (p value for difference ITT 0.29; PP 0.69) (table 2).

If only patients with first-line therapy were included ITT cure rates were 43/45 (96%, 95% CI 91 to 100%) for patients treated with esomeprazole, amoxicillin and levofloxacin and 55/59 (93%, 95% CI 87 to 100%) for patients treated with esomeprazole, clarithromycin and levofloxacin (p value for difference: 0.61).

If only patients with second/third-line therapy were included ITT cure rates were 14/14 (100%) for group I and 4/5 (80%) for group II (p value for difference 0.09).

Side effects

Both regimens were well tolerated, although in the regimen with clarithromycin discontinuation of treatment occurred in two patients. Reasons for discontinuation were nausea in one and rupture of an Achilles tendon in the other patient. When tested, neither of these patients were cured of their infection. Minor side effects occurred in 29% of all patients in group I and in 41% of all patients in group II (p=0.17). Diarrhoea was the most common side effect.

DISCUSSION

The results of this study show that levofloxacin can be used safely for eradication of *H. pylori*. They also show that its use leads to high cure rates in Dutch patients. A limitation of the present study is that it is not a blinded randomised clinical trial. However, treatment allocation was determined only by the date of inclusion, not by patient characteristics. This is confirmed by the comparable baseline characteristics of both groups. Furthermore, cure of *H. pylori* infection is a solid, well-defined endpoint and open studies like ours are well accepted in this field in order to identify new treatment options.

The triple therapy with esomeprazole, amoxicillin and levofloxacin reached a 96% (43/45) per protocol cure rate when used as initial therapy. With the identical therapeutic regimen in primary treatment Antos *et al.* cured 28/30 of patients (93.3%) in France.²² Retreatment after failure of an initial anti-*Helicobacter* therapy is generally considered to be more difficult than initial therapy, but when we employed this triple drug therapy as second-line therapy in eight patients and as third-line therapy in six patients it was successful in all these patients. Most studies in the literature also deal with the use of levofloxacin in second- or third-line therapy.

Several studies have directly compared different levofloxacin-based combinations with several different quadruple combinations in retreatment. Two systematic reviews and meta-analyses have summarised these studies,

and the data suggest that the levofloxacin-based regimens were a good alternative to quadruple therapy.^{16,20} In fact, levofloxacin containing treatments had superior cure rates as compared with the standard quadruple regimens.^{16,20,34} The cure rates achieved with levofloxacin in these studies, however, were somewhat lower than the >95% we have achieved in our study.^{16,20} Furthermore, one study suggested that the levofloxacin-based triple therapy was also superior to rifabutin-based triple therapy, which is another established rescue therapy.²³ Our excellent result with esomeprazole, amoxicillin and levofloxacin for retreatment in patients who failed to be cured with their previous therapy therefore supports this large body of data from the literature.^{14,20,22-29,35} The triple therapy with esomeprazole, clarithromycin and levofloxacin reached a 96% (55/57) per protocol cure rate when used as initial therapy. At present, triple therapy with a PPI, amoxicillin and clarithromycin is usually our primary therapy. After failure of this regimen bacteria resistant to clarithromycin are usually encountered, whereas resistance to amoxicillin is extremely rare.^{30,31} Amoxicillin can therefore be used in retreatment, but microbiologically it is not logical to use clarithromycin again in retreatment. Nevertheless, we cured four out of five patients who had previously failed a PPI, amoxicillin and clarithromycin combination with regimen II. Few studies are available regarding the combination of levofloxacin with clarithromycin or another macrolide.^{24,28} Randomised head-to-head studies of regimen I vs regimen II are unavailable. However, theoretically, primary clarithromycin resistance might have a negative impact on the cure rates of the regimen we used in group II.

At the moment it is not clear whether levofloxacin should be used in seven or ten-day regimens. Some authors have consistently used ten-day therapies and meta-analysis showed this to be superior to seven-day therapy.^{16,20} Our results with seven days of treatment in Dutch patients are already >95% and therefore we do not promote increasing the length of treatment from seven to ten days for the Dutch situation. Most Italian ten-day studies used a lower dose of levofloxacin, either 500 mg once daily or 250 mg twice daily. Others and we chose a higher dose of 500 mg twice daily for seven days and this has been shown to be a well-tolerated and safe dosage schedule.²¹ Therefore, we would at present not recommend using a lower dose.²⁰

A possible threat to the efficacy of levofloxacin is the presence of antimicrobial resistance to fluoroquinolones.³¹ The prevalence of this resistance has been determined in only a limited number of studies. The only Dutch data date back to 1999, when Debets-Ossenkopp reported a primary resistance rate of trovafloxacin of 4.7%.³⁶ In France, resistance to fluoroquinolones increased from 3.3% in 1999 to 17.5% in 2003.³⁷ In 2006, it was reported to be 16.8% in Belgium.³⁸ The high rate of resistance in these countries

probably mirrors the increasing use of quinolones to treat various common infections.³⁹ A well-documented much lower use of quinolones in the Netherlands⁴⁰ as compared with France and Belgium probably results in lower levels of fluoroquinolone resistance in Dutch patients. This might also explain why our cure rates are at the top of what is reported in the literature. The higher dose of levofloxacin, however, is another possible explanation for our relatively high cure rate.

Levofloxacin as an antibiotic is generally well tolerated.¹³ Overall in our study adverse effects were reported by 35% of the patients, but these were most often mild. Twenty-nine percent of patients in group I reported side effects, but they did not lead to discontinuation in any of these patients. Forty-one percent of patients in group II, a higher number in comparison with group I, reported side effects. In two patients, treatment was discontinued, because of extreme nausea and an Achilles tendon rupture. The latter is a known, but rare and severe complication, but in our patient, a 70-year-old man, it healed and had no long-term consequences. According to an investigation in the United States tendon rupture occurs in less than four per million prescriptions of levofloxacin,⁴¹ and it should not therefore be a reason to fear the use of this antibiotic. Based on our data it appears that the combination of levofloxacin with amoxicillin is better tolerated and causes fewer side effects than the combination of levofloxacin with clarithromycin. Then, based on our own experience and our review of the literature, what should be the place of levofloxacin in *Helicobacter* therapy in the Netherlands? According to the Dutch CBO/NHG consensus a triple therapy with a PPI, amoxicillin and clarithromycin should be the initial regimen for treating *H. pylori* infection in the Netherlands. Janssen *et al.* recently reported the prevalence of *H. pylori* antibiotic resistance in the east of the Netherlands. This study shows that primary metronidazole resistance was stable throughout the study period (1997-2002) with a mean prevalence of 1.4%. The prevalence of primary clarithromycin resistance was still very low (mean prevalence 1%).⁴² Therefore, a regimen with amoxicillin and clarithromycin is a logical and microbiologically sound choice for an initial anti-*Helicobacter* therapy in the Netherlands and it should probably remain our initial therapy. It leads to high cure rates and with these high cure rates it is almost impossible to demonstrate superiority with another therapy. An Italian study showed superiority of the regimen we used in group II over standard PPI-triple therapy, but resistance against clarithromycin is much higher in Italy than in the Netherlands.²¹ Levofloxacin-based therapies are an alternative for primary treatment in the Netherlands. However, we would not yet recommend them as initial therapy, especially since data on primary fluoroquinolone resistance of *H. pylori* in the Netherlands are not yet available.

According to the guidelines, all patients who received initial therapy should be tested for cure if urea breath testing is available. Patients also have a desire to know whether or not they are truly cured.^{8,4,25,43} Quadruple therapy is recommended in the Dutch guideline as back-up therapy⁴ but bismuth (De-Nol® or Ranitidine Bismuth Subcitrate (Pylorid®)) is no longer available. In this situation it seems logical to accept a levofloxacin-based regimen as a universal second-line therapy. Those who are not cured after an initial attempt can be retreated with the esomeprazole, amoxicillin, and levofloxacin regimen that we employed in group I. In case of penicillin allergy it is advisable to initially use a seven-day combination of a PPI, clarithromycin 250 mg or 500 mg, and metronidazole 500 mg, all twice daily. If this fails, the levofloxacin regimen we used in group II can be used as rescue therapy. A triple therapy of a PPI with levofloxacin and tinidazole (500 mg twice daily) might be an alternative in this setting.²⁹

CONCLUSION

Seven-day triple therapy with esomeprazole, levofloxacin and either amoxicillin or clarithromycin is very effective and safe for *H. pylori* eradication in the Netherlands. These regimens can be used as first-line therapy and as second-line therapy. The combination with amoxicillin appears to cause fewer side effects. Regimens incorporating levofloxacin provide us with new and long awaited possibilities to treat *H. pylori*. Although it may be too early to promote their use as initial therapy we can, based on our data as well as the literature, already advise the use of these regimens for back up after failed initial therapy.

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