High-dose esomeprazole and amoxicillin dual therapy for first-line *Helicobacter pylori* eradication: a proof of concept study

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**Abstract**

**Background** The prevalence of resistance to clarithromycin and metronidazole has considerably increased, with a corresponding decrease in the eradication rate for *Helicobacter pylori* (*H. pylori*) infection. Primary resistance to amoxicillin is extremely low, and esomeprazole was found to exert a noteworthy antimicrobial activity *in vitro* against *H. pylori*. A dual therapy with high-dose of esomeprazole coupled with high-dose amoxicillin might be therefore an ideal first-line treatment for *H. pylori* eradication. We aimed to assess the efficacy of a first-line 10-day, high-dose dual therapy consisting of amoxicillin and esomeprazole to eradicate *H. pylori* infection.

**Methods** Consecutive naïve *H. pylori*-infected patients, who underwent an upper endoscopy in 4 Italian hospitals due to dyspeptic symptoms and found to be infected at routine histological assessment, were invited to participate. Patients enrolled received a 10-day, high-dose dual therapy comprising esomeprazole (40 mg t.i.d) and amoxicillin (1 g t.i.d.). At least 4 weeks after the end of the treatment a 13C-urea breath test was performed to evaluate the eradication.

**Results** A total of 56 patients agreed to participate in the study and were all followed-up. The overall eradication was 87.5% (95% CI=78.8•96.2), without a statistically significant difference among centres. Overall, 5 (8.9%; 1.5•16.4%) patients complained of side-effects.

**Conclusions** The 10-day, high-dose dual therapy with esomeprazole and amoxicillin might be an effective and safe first-line regimen. The efficacy of a longer 14-day regimen should be tested.

**Keywords** *Helicobacter pylori* infection, dual therapy, esomeprazole, amoxicillin

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of strains of _H. pylori_ resistant to clarithromycin and/or metronidazole. Amoxicillin is a β-lactam antibiotic included in all current therapeutic regimens for _H. pylori_ eradication [11]. Indeed, minimum inhibitor concentration values against _H. pylori_ strains are ranging from 0.06 to 0.25 mg/L [11]. Although amoxicillin resistance and tolerance have been reported in _H. pylori_ isolates [12,13], the primary resistance to amoxicillin is extremely low in several countries, with a prevalence rate as low as <1% (95% CI: 0.06-1.06) and 3% in Europe and the U.S., respectively [7,8]. However, amoxicillin is largely inactivated by low pH values present in the stomach [14,15], so that a simultaneous proton pump inhibitor (PPI) therapy is mandatory [16]. In addition, a deep suppression of gastric acid secretion, allowing to achieve pH value >6, is expected to favor antibacterial activity of amoxicillin in the gastric juice [14]. However, such a condition is rarely achieved in Caucasian subjects with standard dose of PPIs, due to the genetic polymorphism of hepatic P450 cytochrome responsible of PPI metabolism. Indeed, as many as >95% of Caucasians are rapid or intermediate metabolizers of PPIs [17], suggesting that an increased dose is needed in the majority of Caucasian subjects. On the other hand, among PPIs, esomeprazole was found to exert a greater antimicrobial activity _in vitro_ against _H. pylori_ compared to omeprazole, which could help improve the success rate of eradication regimens [18]. Based on these considerations, a dual therapy with high-dose esomeprazole, which increases intragastric pH and exerts a direct anti-bacterial activity, coupled with high-dose amoxicillin, against which primary resistance is extremely low, would be an ideal first-line treatment for _H. pylori_ eradication.

We therefore designed this proof of concept study to assess the efficacy of such a high-dose dual therapy as first-line treatment in _H. pylori_-infected patients.

**Patients and methods**

**Patients**

This was an open-label, study performed in 4 Italian Hospitals (1 Northern; 2 Central, and 1 Southern Italy). In each participating center, consecutive adult (>18 years) patients, who underwent upper endoscopy due to dyspeptic symptoms and found to be infected with _H. pylori_ at routine histological assessment, were invited to participate. Exclusion criteria were: 1) previous _H. pylori_ eradication therapy; 2) known or suspected allergy to penicillin; 3) use of PPI or antibiotics in the previous 4 weeks; 4) previous surgery of upper gastrointestinal tract; 5) severe diseases (cardiovascular, pulmonary, renal or hepatic); 6) malignant disease during the previous 5 years; 7) alcohol abuse or severe psychiatric or neurologic disorders; 8) pregnancy or lactation; and 9) refusal to consent.

**Therapy regimen**

All patients received a 10-day, high-dose dual therapy comprising esomeprazole (40 mg t.i.d) and amoxicillin (1 g t.i.d.). The PPI was given half an hour before breakfast, lunch and dinner, whilst amoxicillin just after these meals. At the end of the treatment, compliance to therapy and reported side-effects were assessed by a personal interview. At least 4 weeks after the end of the treatment a 13C urea breath test (UBT) was performed to evaluate _H. pylori_ eradication rate.

**Statistical analysis**

The eradication rate with 95% confidence intervals was calculated. Before pooling the estimates, a Fisher’s exact test was performed to exclude a significant heterogeneity among the different centers. Based on the study design (pilot study), data of only those patients who took ≥80% of prescribed drugs, and underwent UBT control were considered.

**Results**

A total of 56 (male/female = 32/24; mean age: 51.3±13.7 years) patients agreed to participate in the study. All patients confirmed having taken all the prescribed drugs, but two patients who performed the therapy for 9 and 8 days, respectively. All these patients underwent the scheduled UBT control. As shown in Table 1, _H. pylori_ infection was successfully cured in 87.5% (95% CI=78.8•96.2), without a statistically significant difference among the participating centers. Overall, 5 (8.9%; 1.5•16.4%) patients complained of side-effects (2 vomiting, 2 nausea, and 1 mild diarrhea), but only the 2 patients with vomiting early interrupted the treatment (at 9 and 8 days). All side-effects were self-limited.

**Discussion**

The success rate of standard triple therapies for _H. pylori_ eradication is decreasing worldwide [19], suggesting the need of novel therapy regimens. Since newer agents with elevated activity against such an infection, including resistant strains, are still lacking [10], optimizing the use of available

| Centre | Patients enrolled | Patients cured | Eradication rate, % (95% CI) |
|--------|------------------|----------------|-----------------------------|
| Rome   | 23               | 21             | 91.3                        |
| Latina | 14               | 12             | 85.7                        |
| Foggia | 10               | 8              | 80                          |
| Milan  | 9                | 8              | 88.9                        |
| Total  | 56               | 49             | 87.5 (78.8•96.2)            |

Table 1 _Helicobacter pylori_ eradication rate achieved in different centers.
antibiotics would be advantageous. With this purpose, we tested the efficacy of a first-line, high-dose esomeprazole-amoxicillin dual therapy. The rationale of such a regimen consisted in coupling a deep suppression of acid secretion achieved with high-dose esomeprazole which would favor the efficacy of high-dose amoxicillin for which primary resistance in H. pylori isolates is very uncommon. Our study showed an interestingly high efficacy of this regimen, approaching a 90% success rate in our series. Of note, such a high cure rate was achieved using a regimen lasting only 10 days, suggesting that a longer 14-day therapy could perform better, particularly when considering the high tolerability we observed. Indeed, a 14-day high-dose dual therapy regimen with omeprazole 120 mg and amoxicillin 2.25 g achieved an 89% eradication rate in duodenal ulcer patients [20], and 96% in 126 MALT-lymphoma patients [21]. Likewise, a 95.5% eradication rate was achieved with a high-dose lansoprazole and amoxicillin 2 g first-line therapy in Japan [22]. In addition, a recent study performed in Taiwan showed that a high-dose dual therapy with rabeprazole 20 mg and amoxicillin 750 mg, all given q.i.d. for 14 days, achieved a 95.3% cure rate in naïve patients [23]. Interestingly, high-dose dual therapy with omeprazole 20 mg q.i.d. and amoxicillin 1 g b.i.d achieved a significantly higher eradication rate than 14-day triple therapy in Turkey [24], where achieving H. pylori eradication is notoriously difficult [25]. On the contrary, a disappointing 53.8% success rate was achieved in 13 patients using dexlansoprazole 120 mg and amoxicillin 1 g, both b.i.d. for 14 days [26]. Moreover, the attempt to improve a high-dose dual therapy with esomeprazole 40 mg b.i.d. and amoxicillin 1 g t.i.d for 10 days by adding metronidazole did not appear to be advantageous, the eradication rates being 82.4% and 88.2% at intention-to-treat and per protocol analysis, respectively [27]. Overall, all these observations would suggest that a study testing our proposed high-dose dual regimen with esomeprazole 40 mg and amoxicillin 1 g, both t.i.d., for 14 days is urged. The usefulness of a study is further supported by the high tolerability of such a regimen, for which the incidence of adverse events was reported to be not significantly superior to those observed in the comparison arms [20,22,28].

In conclusion, this is the first Italian study showing that a 10-day, high-dose dual therapy with esomeprazole and amoxicillin could achieve high eradication rates, suggesting that the efficacy of a longer 14-day regimen should be tested.

References

1. McColl KE. Clinical practice. Helicobacter pylori infection. N Engl J Med 2010; 362:1597-1604.
2. Zullo A, Hassan C, Ridola L, et al. Gastric MALT lymphoma: old and new insights. Ann Gastroenterol 2014;27:23-33.
3. Mallfertheiner P, Megraud F, O’Morain CA, et al. Management of Helicobacter pylori infection - the Maastricht IV/Florence Consensus Report. Gut 2012;61:646-664.
4. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol 2007;102:1808-1825.
5. Hunt RH, Xiao SD, Megraud F, et al. Helicobacter pylori in developing countries. World Gastroenterology Organisation Global Guideline. J Gastrointest Liver Dis 2011;20:299-304.
6. Asaka M, Kato M, Takahashi S, et al. Guidelines for the management of Helicobacter pylori infection in Japan: 2009 revised edition. Helicobacter 2010;15:1-20.
7. De Francesco V, Giorgio F, Hassan C, et al. Worldwide H. pylori antibiotic resistance: a systematic review. J Gastrointestin Liver Dis 2010;19:409-414.
8. Megraud F, Coenen S, Versporten A, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62:34-42.
9. De Francesco V, Ierardi E, Hassan C, et al. Helicobacter pylori therapy: present and future. World J Gastrointest Pharmacol Ther 2012;3:68-73.
10. Fiorini G, Zullo A, Gatta L, et al. Newer agents for Helicobacter pylori eradication. Clin Exp Gastroenterol 2012;5:109-112.
11. De Francesco V, Zullo A, Hassan C, et al. Mechanisms of Helicobacter pylori antibiotic resistance: an updated appraisal. World J Gastrointest Pathophysiol 2011;2:35-41.
12. van Zwet AA, Vandenbroucke-Grauls CM, Thijs JC, et al. Stable amoxicillin resistance in Helicobacter pylori. Lancet 1998;352:1595.
13. Dore MP, Osato MS, Realdi G, et al. Amoxicillin tolerance in Helicobacter pylori. J Antimicrob Chemother 1999;44:47-54.
14. Grayson ML, Ellipoulois GM, Ferraro MJ, et al. Effect of varying pH on the susceptibility of Campylobacter pylori to antimicrobial agents. Eur J Clin Microbiol Infect Dis 1989;8:888-889.
15. Lambert JR. Pharmacology of the gastric mucosa: a rational approach to Helicobacter pylori therapy. Gastroenterology 1996;111:521-523.
16. Goddard AF, Jessa MJ, Barrett DA, et al. Effect of omeprazole on the distribution of metronidazole, amoxicillin, and clarithromycin in human gastric juice. Gastroenterology 1996;111:358-367.
17. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. Eur J Clin Pharmacol 2008;64:935-951.
18. Gatta L, Perna F, Figura N, et al. Antimicrobial activity of esomeprazole versus omeprazole against Helicobacter pylori. *J Antimicrob Chemother* 2003;51:439-442.
19. Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013;347:f587.
20. Bayerdorffer E, Miehlke S, Mannes GA, et al. Double-blind trial of omeprazole and amoxicillin to cure Helicobacter pylori infection in patients with duodenal ulcers. *Gastroenterology* 1995;108:1412-1417.
21. Zullo A, Hassan C, Andriani A, et al. Eradication therapy for Helicobacter pylori in patients with gastric MALT-lymphoma: a pooled data analysis. *Am J Gastroenterol* 2009;104:1932-1937.
22. Furuta T, Shirai N, Kodaika M, et al. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of *H. pylori*. *Clin Pharmacol Ther* 2007;81:521-528.
23. Yang JC, Lin CJ, Wang HL, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for Helicobacter pylori Infection. *Clin Gastroenterol Hepatol* 2015;13:895-905.
24. Ince AT, Tozlu M, Baysal B, Şentürk H, Arıcı S, Özden A. Yields of dual therapy containing high-dose proton pump inhibitor in eradication of *H. pylori* positive dyspeptic patients. *Hepatogastroenterology* 2014;61:1454-1458.
25. Zullo A, De Francesco V, Hassan C, et al. Modified sequential therapy regimens for Helicobacter pylori eradication: a systematic review. *Dig Liver Dis* 2013;45:18-22.
26. Attumi TA, Graham DY. High-dose extended-release lansoprazole (dexlansoprazole) and amoxicillin dual therapy for Helicobacter pylori infections. *Helicobacter* 2014;19:319-322.
27. Sánchez-Delgado J, García-Iglesias P, Castro-Fernández M, et al. High-dose, ten-day esomeprazole, amoxicillin and metronidazole triple therapy achieves high *Helicobacter pylori* eradication rates. *Aliment Pharmacol Ther* 2012;36:190-196.
28. Shirai N, Sugimoto M, Kodaika C, et al. Dual therapy with high doses of rabeprazole and amoxicillin versus triple therapy with rabeprazole, amoxicillin, and metronidazole as a rescue regimen for *Helicobacter pylori* infection after the standard triple therapy. *Eur J Clin Pharmacol* 2007;63:743-749.