Arch Clin Infect Dis. 2014 June; 9(3): e18549. DOI: 10.5812/archcid.18549

Published online 2014 June 25. **Research Article**

Furazolidone-Based Quadruple Therapy for Eradication of *Helicobacter pylori* Infection in Peptic Ulcer Disease

Rahim Raoufi Jahromi [1]; Jamal Mirzaei [2]; Jalil Rajabi [2,*]; Seyed Javad Hoseini Shokouh [2]; Taraneh Liaghat [1]

[1]Department of Infectious Diseases, Jahrom University of Medical Sciences, Jahrom, IR Iran
[2]Infectious Disease Research Center, Department of Infectious Diseases, Aja University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Jalil Rajabi, Infectious Disease Research Center, Aja University of Medical Sciences, Tehran, IR Iran. Tel: +98-9124450255, Fax: +98-2144066531, E-mail: rajabi_jalil@yahoo.com

Received: April 14, 2014; **Accepted:** May 30, 2014

Background: *Helicobacter pylori* is the main pathogenic factor for chronic gastritis and peptic ulcer disease. Therefore, its successful eradication is important in the disease management. Multiple first-line treatments have been employed; the eradication rates in the most successful regimens have been 75%-92%. Primary bacterial resistance to antibiotics and patient compliance are two main cause of therapy failure. Furazolidone with a broad spectrum of antimicrobial activities is widely used in the treatment of bacterial and protozoal infections in both humans and animals, which could also be used in treatment of *H. pylori* infection.

Objectives: This study was designed to evaluate the efficacy of the therapeutic regimen containing furazolidone in comparison with a standard regimen against *H. pylori*.

Materials and Methods: In this randomized clinical trial, 110 patients with a positive urease breath test (UBT) were selected and randomly divided into two equal groups. The first group received the standard regimen consisting of clarithromycin (500 mg Q12h), amoxicillin (1 g Q12) and a proton pump inhibitor (PPI) (omeprazole 20 mg BID). The second group received bismuth subcitrate (120 mg Q6h), furazolidone (100 mg Q6h) and tetracycline (250 mg Q6h) and a PPI (omeprazole 20 mg BID) for two weeks. UBT was performed again for all the patients two months after completing.

Results: UBT was negative in 83.6% of patients in the standard group two months after the end of the treatment. Eradication of *H. pylori* was reported in 94.5% of patients in the experimental group. No significant relationship between age and eradication of *H. pylori* was observed in both groups. Nausea and vomiting was reported in 5.45% of patients treated with our experimental regimen. These symptoms were tolerable and the treatment was completely continued. No adverse effect was recorded in the standard group. Moreover, no relationship was observed between gender and eradication of *H. pylori* in both groups. Finally, despite a better therapeutic response to our experimental group in comparison with the standard one, no statistically significant difference was observed (P = 0.067).

Conclusions: Based on our finding in this study and similar studies in different parts of the world, furazolidone could be prescribed as an effective antibiotic against *H. pylori* in patients with gastritis.

Keywords: Gastritis; Furazolidone; *Helicobacter pylori*

1. Background

There is a close relation between gastrointestinal diseases and *Helicobacter pylori*. This microorganism is the main pathogenic factor of chronic gastritis and peptic ulcer disease. In addition, the initiating factor in gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma is *H. pylori* (1). Finding this microorganism as a causative agent of peptic ulcer disease (PUD) has revolutionized the scientific understanding of the condition treatment (2). Because of the integral role of *H. pylori* in pathogenesis of PUD, its successful eradication is important in management of this disease (3-6), and substantially, the risk of ulcer recurrence and rebleeding could be reduced (3, 4). There has been a research focus to eradicate this microorganism for effective treatment of the above diseases (7). Multiple first-line treatments have been employed, and the eradication rates in the most successful regimens were from 75% to 92% (5).

There is a universal standard triple therapy with a proton pump inhibitor (PPI) or bismuth, amoxicillin and metronidazole or clarithromycin. Unfortunately, because of the widespread use of antibiotics, an increasing resistance to *H. pylori*, especially to metronidazole and clarithromycin has been resulted. "Legacy triple therapy", recommended by the Maastricht Ⅲ consensus report, has disappointingly demonstrated low success rates (i.e. below 80%) worldwide (7). Primary bacterial resistance to antibiotics and patient compliance are two main cause of therapy failure. Moreover, there are some restrictions in the use of some expensive drugs such as clarithromycin and quinolones in developing countries,

where a high prevalence of primary metronidazole resistance is present (8).

The high prevalence of *H. pylori* infection in adults over 35 years old (near 90%) has been shown in multiple seroepidemiological studies in different parts of Iran. There has been much lower eradication rate of *H. pylori* in this country than the rates reported from western and developed countries. Additionally, a high rate of metronidazole resistance (37%) and an increasing rate of resistance to clarithromycin have emerged (9). Therefore, it has been suggested to use furazolidone-based treatment by the World Gastroenterology Organization and Latin-America guidelines, to overcome these limitations in developing countries (10, 11). This drug is a synthetic nitrofuran with a broad spectrum of antimicrobial activities, widely used in treatment of bacterial and protozoal infections in both humans and animals (12). In spite of the low cost of the drug, some adverse effects, such as a molecule harboring a potential carcinogenetic effect, might influence the drug efficacy (13-19).

2. Objectives

Increasing resistances of *H. pylori* to different antimicrobial drugs have encouraged scientists to find new effective therapeutic regimens. Using forgotten effective antimicrobial drugs in therapeutic regimens could be an effective solution for this problem. In this study, the efficacy of a therapeutic regimen containing furazolidone in comparison with a standard regimen against *H. pylori* was evaluated.

3. Materials and Methods

In this randomized clinical trial, each patient with persistent dispepsia, referred to Honari Clinic in Jahrom, Iran during a period of six mounts (from July to December 2012), swallowed a 14C-urea capsule for urease breath test (UBT) after a six-hour fasting period. Thereafter, patients laid down and changed sides every five minutes. Breath samples were collected from the subjects 15 minutes after the 14C-urea consumption. The samples were collected and counted using the Heliprobe method. In this method, patients exhaled into a special dry cartridge system (Heliprobe breath card) at the 15th minute. The activities of the cartridges were counted using a small designated GM (Geiger-Müller) counter system (Heliprobe analyzer); 110 patients with a positive UBT were selected. Neither of them had a history of using proton pump inhibitor (PPI) or H2 Blocker during the previous week nor using antibiotics during the previous mount. They were randomly divided into two equal groups. The first group received the standard regimen consisting of clarithromycin (500 mg Q12h), amoxicillin (1 g Q12) and a PPI (omeprazole 20 mg BID). The second group received bismuth subcitrate (120 mg Q6h), furazolidone (100 mg Q6h) and tetracycline (250 mg Q6h) and a PPI (omeprazole 20 mg BID). The treatment duration in both groups was two weeks. UBT was performed again for all the patients two months after completing the treatment to evaluate and compare the efficacy of these two regimens. Any patient with intolerance to these two regimens was excluded from the study. All the data was registered in special forms and analyzed with SPSS version 18 software using chi-square and Fisher tests and variance analysis.

4. Results

A total of 110 patients, 20-70 years old, with mean age of 36.18 ±9.43 years old were studied. They were divided into five age groups (Table 1). Most of the patients belonged to the 30-40-year-old group (40%); 50 patients (45.5%) were male and 60 (55.5%) were female; 55 patients were treated with standard regimen for two weeks, among which, the UBT results were negative for 46 (83.6%), while it was still positive in 9 (5.5%), two months after the end of the treatment. There was no statistically significant relationship between age and eradication of *H. pylori* in the standard regimen group (P = 0.41). In the second group in which 55 patients were treated with our experimental regimen, only 3 (5.5%) had positive UBT results two months after the end of the treatment and eradication of *H. pylori* was reported in 52 (94.5%) patients based on negative UBT results. In this group, the highest eradication rate of *H. pylori* was reported in 30-40-year-old patients. However, there was no significant relationship between age and eradication of *H. pylori* in our experimental regimen group, too (P = 0.21).

Nausea and vomiting was reported in 3 (5.45%) patients treated with our experimental regimen. These symptoms were tolerable and the treatment was completely continued. No adverse effect was recorded in the standard group. Moreover, no relationship was observed between gender and eradication of *H. pylori* in both groups (P = 0.5 in the standard group and P = 0.44 in the experimental group). Finally, despite a better therapeutic response to our experimental group in comparison with the standard group, no statistically significant difference was observed (P = 0.067).

Table 1. Age Distribution of the groups

Group No.	Age Group Range, y	No. (%)
1	20-30	36 (32.7)
2	30-40	44 (40)
3	40-50	21 (19.1)
4	50-60	8 (7.3)
5	60-70	1 (9)
Total		110 (100)

5. Discussion

Different types of drugs such as antibiotics, antacids and metal preparations have been effective against *H. pylori* infection in multiple clinical trials. The usefulness

of many antibiotics such as tetracycline, clarithromycin, amoxicillin, metronidazole and furazolidone on this bacterium with bactericidal or bacteriostatic effects has been proven (20). Reduction in the eradication rate with the standard triple therapy (PPI-clarithromycin-amoxicillin or metronidazole) (21) to unacceptable levels (i.e. 80% or less) has been observed in several recent clinical trials and meta-analyses (22, 23). This drug resistance could be the result of overuse and inappropriate consumption of these drugs as well as frequent anti-*H. pylori* treatment failures (24) Therefore, using less frequently used antibiotics which may be less likely to induce antibiotic resistance, which could be a logical strategy.

Despite the lack of routine use of furazolidone in the standard regimen against *H. pylori*, its high sensitivity rate (100%) (25) and significant effect on *H. pylori* conducted our team to include this drug in therapeutic regimen of our patients. It was shown in various studies that an eradication rate around 80% was achievable by a furazolidone-based combination therapy (26-28). In our study, the eradication rate of our experimental regimen containing furazolidone was 94.5%, which was more successful than some other recent similar studies in Iran (29, 30). Our results were similar to another study in Shiraz, Iran, in which a therapeutic regimen containing furazolidone and clarithromycin achieved the most eradication rate against *H. pylori* and it was advised to use these medications to treat Iranian people with gastritis (31).

There are some other studies confirming the effectiveness of this drug against *H. pylori*. In Bahari's study in Zahedan, Iran, a regimen containing furazolidone was more effective (85%) than another regimen without it (80%) (32). Moreover, in Babol, Iran, a regimen containing furazolidone achieved a higher rate (60%) than the other one (54.3%) (33). In Talebi's study in Iran, *H. pylori* resistance to different antibiotics was evaluated. In this survey, the least resistance was reported against furazolidone, tetracycline and clarithromycin, and the bacteria showed the highest resistance against metronidazole and amoxicillin (34). This high resistance rate against metronidazole was confirmed by Tirgar's study on 101 patients (35). An acceptable reason for the high rate in both groups of our study might be due to not using metronidazole in both regimens. Therefore, it could be advised not to use metronidazole as an ingredient of therapeutic regimen against *H. pylori* for Iranian people.

Unfortunately, adverse effects of furazolidone may lead to interruption of treatment. This could be the main cause limiting the usage of this medication (27-30, 36). In our study, nausea and vomiting were reported in 3 (5.45%) patients who received furazolidone. This finding was similar to Ghadir's study results from Iran, who reported some adverse effects in six of 86 patients (7%) treated with a therapeutic regimen contain furazolidone. Their symptoms were weakness, nausea, anorexia, and dizziness (30). Additionally, Ma in China reported dizziness, nausea and vomiting as the most common adverse effects in the furazolidone group. These reactions were mild and well tolerated and all the patients in that study were able to complete the entire therapy duration (20). Similarly, in Fakheri's study, the number of patients who discontinued treatment with a furazolidone-containing regimen was not significant (29). Therefore, it could be concluded that side effects of this drug are not significant and could often be well tolerated by patients.

Based on our findings in this study and similar studies in different parts of the world, furazolidone could be prescribed as an effective antibiotic against *H. pylori* in patients with gastritis. However, adverse effect should be mentioned and monitored by physicians. Therefore, it could be recommended to use different antibiotics against *H. pylori* infection alternatively to decrease the chance of antibiotic resistance against this bacterium.

Funding/Support

This research was supported by a grant from the Infectious and Tropical Diseases Research Center of Jahrom University of Medical Sciences.

References

1. Cheng H, Hu FL, Li J. [Influence of resistance of Helicobacter pylori to antibiotics on the Helicobacter pylori eradication regimens]. *Zhonghua Yi Xue Za Zhi.* 2006;**86**(38):2679–82.
2. Marshall BJ. The 1995 Albert Lasker Medical Research Award. Helicobacter pylori. The etiologic agent for peptic ulcer. *JAMA.* 1995;**274**(13):1064–6.
3. Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol.* 2004;**99**(9):1833–55.
4. Ables AZ, Simon I, Melton ER. Update on Helicobacter pylori treatment. *Am Fam Physician.* 2007;**75**(3):351–8.
5. Howden C. *Helicobacter pylori-related peptic ulcer disease causation, diagnosis, treatment and complications.* Evidence-based gastroenterology editor. BC Decker: Hamilton; 2002. pp. 79–101.
6. Massarrat S, Saberi-Firoozi M, Soleimani A, Himmelmann GW, Hitzges M, Keshavarz H. Peptic ulcer disease, irritable bowel syndrome and constipation in two populations in Iran. *Eur J Gastroenterol Hepatol.* 1995;**7**(5):427–33.
7. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? *Ann Intern Med.* 2009; **151**(2):121–8.
8. Zullo A, Ierardi E, Hassan C, De Francesco V. Furazolidone-based therapies for Helicobacter pylori infection: a pooled-data analysis. *Saudi J Gastroenterol.* 2012;**18**(1):11–7.
9. Siavoshi F, Pourkhajeh AH, Merat S. Susceptibility of various strains of Helicobacter pylorito selected agents. *Arch Iranian Med.* 2000;**3**:60–3.
10. World Gastroenterology Organisation Global Guideline: Helicobacter pylori in developing countries. *J Clin Gastroenterol.* 2011;**45**(5):383–8.
11. Coelho LG, Leon-Barua R, Quigley EM. Latin-American Consensus Conference on Helicobacter pylori infection. Latin-American National Gastroenterological Societies affiliated with the Inter-American Association of Gastroenterology (AIGE). *Am J Gastroenterol.* 2000;**95**(10):2688–91.
12. Treiber G, Ammon S, Malfertheiner P, Klotz U. Impact of furazolidone-based quadruple therapy for eradication of Helicobacter pylori after previous treatment failures. *Helicobacter.* 2002;**7**(4):225–31.
13. Roghani HS, Massarrat S, Shirekhoda M, Butorab Z. Effect of dif-

ferent doses of furazolidone with amoxicillin and omeprazole on eradication of Helicobacter pylori. *J Gastroenterol Hepatol.* 2003;**18**(7):778–82.
14. Malekzadeh R, Merat S, Derakhshan MH, Siavoshi F, Yazdanbod A, Mikaeli J, et al. Low Helicobacter pylori eradication rates with 4- and 7-day regimens in an Iranian population. *J Gastroenterol Hepatol.* 2003;**18**(1):13–7.
15. Ahmed HH, El-Aziem SH, Abdel-Wahhab MA. Potential role of cysteine and methionine in the protection against hormonal imbalance and mutagenicity induced by furazolidone in female rats. *Toxicology.* 2008;**243**(1-2):31–42.
16. Ali BH. Pharmacological, therapeutic and toxicological properties of furazolidone: some recent research. *Vet Res Commun.* 1999;**23**(6):343–60.
17. Jin X, Tang S, Chen Q, Zou J, Zhang T, Liu F, et al. Furazolidone induced oxidative DNA damage via up-regulating ROS that caused cell cycle arrest in human hepatoma G2 cells. *Toxicol Lett.* 2011;**201**(3):205–12.
18. De Francesco V, Ierardi E, Hassan C, Zullo A. Furazolidone therapy for Helicobacter pylori: is it effective and safe? *World J Gastroenterol.* 2009;**15**(15):1914–5.
19. De Francesco V, Ierardi E, Hassan C, Zullo A. Is furazolidone therapy for Helicobacter pylori effective and safe? *Dig Dis Sci.* 2009;**54**(10):2298–9.
20. Ma HJ, Wang JL. Quadruple therapy for eradication of Helicobacter pylori. *World J Gastroenterol.* 2013;**19**(6):931–5.
21. Snyder J. Multiple forms of exploitation in international research: the need for multiple standards of fairness. *Am J Bioeth.* 2010;**10**(6):40–1.
22. Gisbert JP, Pajares R, Pajares JM. Evolution of Helicobacter pylori therapy from a meta-analytical perspective. *Helicobacter.* 2007;**12 Suppl 2**:50–8.
23. Miura M, Satoh S, Tada H, Habuchi T, Suzuki T. Stereoselective metabolism of rabeprazole-thioether to rabeprazole by human liver microsomes. *Eur J Clin Pharmacol.* 2006;**62**(2):113–7.
24. Megraud F. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut.* 2004;**53**(9):1374–84.
25. Branca G, Spanu T, Cammarota G, Schito AM, Gasbarrini A, Gasbarrini GB, et al. High levels of dual resistance to clarithromycin and metronidazole and in vitro activity of levofloxacin against Helicobacter pylori isolates from patients after failure of therapy. *Int J Antimicrob Agents.* 2004;**24**(5):433–8.
26. Malekzadeh R, Ansari R, Vahedi H, Siavoshi F, Alizadeh BZ, Eshraghian MR, et al. Furazolidone versus metronidazole in quadruple therapy for eradication of Helicobacter pylori in duodenal ulcer disease. *Aliment Pharmacol Ther.* 2000;**14**(3):299–303.
27. Forta LC, da CMP, Luz CR. Helicobacter pylorieradication using tetracycline and furazolidone versus amoxicillin and azithromycin lansoprazole-based triple therapy: an open randomized clinical trial. *Arq Gastroent J.* 2005;**42**:111–5.
28. Lu H, Zhang DZ, Hu PJ, Li ZS, Lu XH, Fang XC, et al. One-week regimens containing ranitidine bismuth citrate, furazolidone and either amoxicillin or tetracycline effectively eradicate Helicobacter pylori: a multicentre, randomized, double-blind study. *Aliment Pharmacol Ther.* 2001;**15**(12):1975–9.
29. Fakheri H, Merat S, Hosseini V, Malekzadeh R. Low-dose furazolidone in triple and quadruple regimens for Helicobacter pylori eradication. *Aliment Pharmacol Ther.* 2004;**19**(1):89–93.
30. Ghadir MR, Shafaghi A, Iranikhah A, Pakdin A, Joukar F, Mansour-Ghanaei F. Furazolidone, amoxicillin and omeprazole with or without bismuth for eradication of Helicobacter pylori in peptic ulcer disease. *Turk J Gastroenterol.* 2011;**22**(1):1–5.
31. Saberi-Firoozi M, Nejabat M. Experiences with Helicobacter Pylori Treatment in Iran. *IJMS.* 2006;**31**:4–11.
32. Bahari A, Nezam SK, Karimi M. The comparison of two combination antibiotic [(OAB-T) VS (OAB-F)] regimen trophy in peptic ulcer and dyspepsia patients. *Tabib shargh J.* 2007;**9**(4):237–46.
33. Kashifard M, Taheri H, Barzkar M. Comparison the efficacy of furazolidone and Amoxicillin with Metronidazole and Amoxicillin in Quadruple therapy regimen with average dosage and duration against H.pylori. *Babol Medic Sci J.* 2006;**8**(2):24–31.
34. Talebi Bezminabadi A, Mohabati Mobarez A, Aiami AGH, Rafiee A, Taghwaii T. Evaluation on antibiotic resistance of helicobacter pylori isolated from patients admitted to tooba medical center, Sari. *Mazandaran Medic Sci J.* 2009;**19**(70):26–32.
35. Tirgar Fakheri H, Malekzadeh R, Hosseini VR. Eradication of helicobacter pylori using low dose furazolidone in triple and quadruple therapies versus metronidazole in triple therapy in deodenal ulcer patients. *Mazandaran Medic Sci J.* 2003;**13**(40):51–60.
36. Khatibian M, Ajvadi Y, Nasseri-Moghaddam S, Ebrahimi-Dariani N, Vahedi H, Zendehdel N, et al. Furazolidone-based, metronidazole-based, or a combination regimen for eradication of Helicobacter pylori in peptic ulcer disease. *Arch Iran Med.* 2007;**10**(2):161–7.