Original Article

Efficacy of short-duration Furazolidone in two different quadruple regimens for H. pylori eradication

Hafez Tirgar Fakheri[1], MoloudFakhri[2], Soheila Shahmohammadi[3]

ABSTRACT

Objective: To assess the efficacy and tolerability of using high dose Furazolidone just during the first week of two different quadruple regimens in eradicating H. pylori.

Methodology: One-hundred sixty patients with duodenal ulcer and positive H. pylori infection were randomly allocated into two groups. Group A received (OAM-F) omeprazole (20 mg BID), amoxicillin (1gr BID), metronidazole (500mg BID) for two weeks and Furazolidone (200 mg BID) just during the first week. Patients in group B received (OAB-F) omeprazole (20 mg BID), amoxicillin (1 gr BID), bismuth subcitrate (240 mg BID) for two weeks and Furazolidone (200 mg BID) in the first week.

Results: The eradication rates by per-protocol and intention-to-treat analyses were 86.36% and 80% in group A and 90.27% and 86.3% in group B, respectively. Severe side effects of the drugs were more prevalent in group A compared with group B (12.8% against 2.5%)

Conclusions: One-week Furazolidone combined with two-week Omeprazole, amoxicillin and bismuth subcitrate is a safe and cost effective regimen to eradicate of H pylori infection in Iran.

KEYWORDS: Furazolidone, Quadruple regimen, H. pylori eradication.

Pak J Med Sci July - September 2011 Vol. 27 No. 4 887-891

How to cite this article:

Fakheri HT, Fakhri M, Shahmohammadi S. Efficacy of short-duration Furazolidone in two different quadruple regimens for H. pylori eradication . Pak J Med Sci 2011;27(4):887-891

1. Hafez Tirgar Fakheri, MD,
Associate Professor,
Department of Gastroenterology,
2. Moloud Fakhri, MSc,
Senior Lecturer, Member of Faculty,
Department of Midwifery,
Nasibeh Nursing & Midwifery School,
3. Soheila Shahmohammadi, MSc,
CRNA, Research fellow,
Nursing and Midwifery Research Center,
Nasibeh Nursing & Midwifery School,
1-3: Mazandaran University of Medical Sciences,
Sari, Iran.

Correspondence:

Hafez TirgarFakheri, MD,
Associate Professor,
Department of Gastroenterology,
Imam Khomeini Hospital,
Amir Mazandarani Boulevard,
P.O.Box: 48166-33131,
Sari, Iran.
E-mail: fakher42@yahoo.com

* Received for Publication: August 15, 2010
* Revision Received: July 16, 2011
* Second Revision Received: July 19, 2011
* Final Revision Accepted: August 6, 2011

INTRODUCTION

Helicobacter pylori is a human pathogen with global interest. The pathogen is thought to be present in about half of the people in the world,[1] and it is the major cause of chronic gastritis, peptic ulcer, low grade gastric mucosa–associated lymphoid tissue lymphoma, atrophic gastritis and gastric adenocarcinoma.[2-5]

The optimal regimen is defined to be the one which can eradicate H. pylori infection in >90% of cases by per-protocol (PP) and >80% by intention-to-treat (ITT) analyses.[6]

Following a study published by WHO in 1984, H. Pylori was considered as a grade-I carcinogen. Although there are several studies performed to assess the effects of different therapeutic regimens on H. pylori eradication, the optimal therapeutic strategy is still unclear. At present, there are two recommended regimens including triple or quadruple therapy. The triple H. pylori regimen is consisted of

omeprazole, clarithromycin, and amoxicillin or metronidazole being recommended for 10-14 days in USA and 7 days in Europe.[7,8] The quadruple treatment regimen for H. pylori is composed of a proton pump inhibitor (PPI), tetracycline, metronidazole and bismuth that are given for 10-14 days .In Asian countries, H. pylori eradication is more difficult and 2 weeks regimen is needed in general.[9,10]

In Iran there is high prevalence of H. pylori infection among adults older than 35 years (>90%) [11], high resistance to metronidazole (55.6%) and the high cost of clarithromycin, it seems that the therapeutic regimens suggested by the developed countries may not be ideal in this country. One of the suitable approaches is to administer different antibiotics with varying combinations, dosages and durations of treatment. These antibiotics should be selected according to the resistance pattern and also cost must be taken into account.

In one of our previous studies, high dose Furazolidone was administered in a quadruple therapy for two weeks. Although the eradication rate by the mentioned study was high (90%), the side effects of the treatment were also considerable particularly in the second week of treatment.[13] Consequently, in another study, Furazolidone was simultaneously used in a triple regimen and a quadruple regimen comprising low dose Furazolidone. But none of these two regimens reached an ideal H. pylori eradication rate.[14] So we decided to assess the efficacy and tolerability of short-duration high-dose Furazolidone in two different quadruple regimens.

METHODOLOGY

The present randomized clinical trial was performed on 160 patients whose duodenal ulcer was documented by upper GI endoscopy and H. pylori infection was confirmed by biopsy from the antrum and rapid urease test (RUT) at Imam Khomeini hospital in Sari/ Northern Iran during 2008 to 2009. Patients less than 18 years old, or those with clinical significant comorbidity such as hepatic, cardiovascular and renal diseases, neoplastic diseases, coagulopathies, history of gastric surgery, pregnancy and lactation, G6PD deficiency, history of allergy to the drugs used in the study were excluded from the study.

The study was approved by ethic committee of Mazandaran University of Medical Sciences and informed consent was taken from all participants in this survey. In addition to demographic characteristics, cigarette smoking, non-steroidal anti-inflammatory drugs (NSAIDs) consumption and history of upper gastrointestinal bleeding (UGIB) were recorded. Besides, the size and number of duodenal ulcer based on endoscopy and the presence of bulb deformity were also recorded. Eligible patients were divided randomly into two equal groups (80 patients in each group).Group A received (OAM-F) omeprazole capsules 20 mg, amoxicillin capsules 1gr, metronidazole tablets 500 mg twice daily for two weeks and Furazolidone tablets 200 mg twice daily just during the first week. Patients in group B received omeprazole tablets 20 mg, amoxicillin capsules 1gr, bismuth subcitrate tablets 240 mg twice daily for two weeks and Furazolidone tablets 200 mg twice daily in the first week only. In order to increase compliance to treatment, patients were trained how to use the medications and were asked to avoid some special foods due to MAO inhibitory effect of Furazolidone.

The patients were also asked to record side effects of the drugs each day and to call the physician for continuation or discontinuation of the drugs in cases of severe side effect. At the end of therapeutic period, patients were visited regarding any side effects and the amount of consumed drugs. Severity of the side effects of the drugs was scored from 0-3 as follow: 0 was considered as experiencing no side effect, score 1 as mild side effect, moderate and severe were also scored 2 and 3, respectively. If the patients took more than 80% of the medication correctly, the compliance would be considered as excellent. Using 60-80% of the recommended drugs was considered fair and less than 60% was considered bad compliance. Twelve weeks after the end of treatment, both studied groups underwent C_{14}- Urea Breath Test (UBT). The eradication rates were analyzed and compared between the two groups using SPSS statistical software (version 11).

RESULTS

One hundred sixty patients were randomly divided into two equal groups. Demographic characteristics of the patients did not statistically differ between the (Table-I). The eradication rates were 86.36% in group A and 90.27% in group B by per protocol (PP) analysis. According to the results, there was no significant difference between the two groups with regard to eradication rate of H pylori. From total of 160 patients, 138 patients (66 in group A and 72 in group B) completed the study and carried out UBT 12 weeks after the end of treatment. Seven patients (3 in group A and 4 in group B) did not perform UBT, 7 patients (6 in group A and 1 in group B) did not tolerate the regimen, and 8 patients (5 in

Table-I: Patients Demographic & clinical Characteristics and endoscopic findings of the patients.

Variables	*Group A (OAM2+F1)*	*Group B (OAB2+F1)*
Male/Female (N %)	53 / 27	52 / 28
Age (Mean ± SD) (years)	37.48±11.6	35.34±10.5
Smokers (N %)	26 (32)	23 (28.7)
History of GI bleeding (N %)	10(6.25%)	13(8.12%)
History of NSAID consumption (N%)	14 (17)	14 (17)
Ulcer Diameter (Mean ± SD) (mm)	9.27±0.2	9.29±0.2
Bulb deformity (N %)	46 (57)	49 (61)

group A and 3 in group B) had no good compliance. The method of follow up and efficacy of treatment were shown in Figure-1.

Frequency and severity of the drug side effects are shown in Table-II. The most frequent complications were nausea, vomiting, dizziness, bitterness and headache. Severe side effects of the drugs were more prevalent in group A compared with group B (12.8% against 2.5%, p-value < 0.05). Six patients in group A discontinued the regimen due to severe side effects including headache, fever and vomiting in one case, fever and vomiting in one case, chest pain, back pain and epigastric pain in three patients, anorexia and anxiety in one case. In group B, only one patient discontinued the regimen due to back pain and epigastric pain.

DISCUSSION

The eradication rates of H pylori with recommended regimens are much lower in developing countries than the rates reported from the developed ones.[15] The presence of difference in H. pylori eradication rates among various geographic regions is obvious.[16,17] The reasons for these differences include the pathogenic differences of H pylori strain, difference in antibiotic resistance, the kind of treatment regimens and the duration of treatment and pharmacogenetic differences in drug metabolism.[17]

Furazolidone is a synthetic nitrofuran derivative with bactericidal and enzyme inhibitory activity when used against Gram-positive and Gram-negative bacteria and it is well absorbed in the intestine (95%) and has rapid distribution and metabolism.[18] Furazolidone- resistant strains appear to be rare or non-existent in many areas of the world.[19] Furazolidone has been used successfully as a first line treatment for H pylori eradication in many studies,[13,14,20,21] and also is used effectively in rescue regimens for H. pylori eradication.[22-25] At present in Iran, about 55.6% of H. pylori isolates are resistant to metronidazoles, 38.1% to tetracycline, 7.3% to clarithromycin and 7.3% are resistant to amoxicillin. While resistance rates of H.pylori isolates to Furazolidone is 4.5%.[12] Therefore, Furazolidone is a suitable drug even as a first line treatment in combination with other drugs in quadruple therapy regimens for eradication of H pylori in Iran. Clinical

Table-II: Adverse effects reported by the patients during treatment.

Adverse effects	*Group AOAM2+F1 n=78*	*Group BOAB2+F1 n=80*	*Total n=158*
Headache	5	3	8
Dizziness	7	6	13
Fever	2	0	2
Nausea & Vomiting	12	11	23
Abdominal pain	3	3	6
Drowsiness	1	1	2
Malaise	3	4	7
Bitterness	4	6	10
Flatulence	2	0	2
Anorexia	1	2	3
Anxiety	1	1	2
Epigastric pain	3	1	4
Glositis	1	0	1
Chest pain	1	0	1
Back pain	1	1	2
Dry mouth	1	0	1
Water brush	0	1	1
Severity of side-effects N (%)			
None	49(62.8)	58(72.5)	107(67.7)
Mild	11(14.1)	12(15)	23(14.6)
Moderate	8(10.3)	8(10)	16(10.1)
Severe	10(12.8)	2(2.5)	12(7.6)

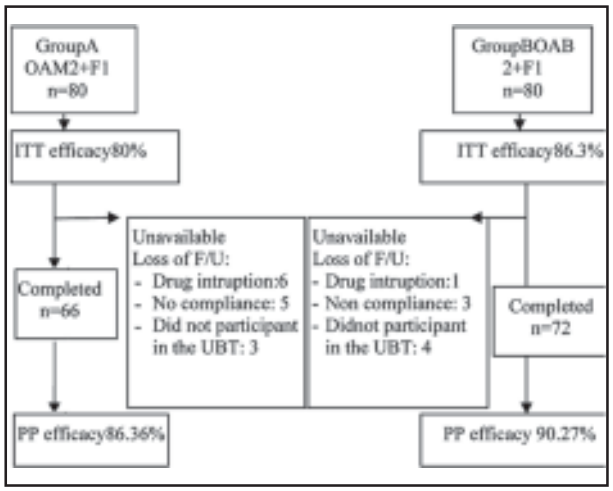

Fig-1: Method of follow up and efficacy of treatment in both groups.

experience about use of Furazolidone in European countries is limited, and it is only about Furazolidone-based rescue regimen. When Furazolidone is administered with 1 or 2 other antibiotics and an anti acid, it results in an eradication rate > 80%.[26,27] Although, Furazolidone provides an excellent improvement in eradication rate of H pylori infection, however, its use has not become wide spread due to the side effects that appear in the second week of treatment leading to limitation or discontinuation of the drug in some cases.[13]Furazolidone with a dose less than 400 mg/ day had less side effect but the efficacy of the drug in H pylori eradication was decreased.[14]

In a study by Khatibian et al, administration of omeprazole, amoxicillin, bismuth subcitrate for two weeks and Furazolidone in the first week and metronidazole in the second half of therapeutic period was as effective as the quadruple regimen containing Furazolidone, and showed less side effects.[28]

Hasan et al reported that a regimen containing furazolidone for one week in combination with omeprazole, amoxicillin and bismuth for two weeks was safe and cost- effective in H pylori eradication. However, substitution of furazolidone by metronidazole in second week of treatment could not increase the eradication rate of H pylori.[29]

If we consider H. pylori infection as an infectious disease, the ideal regimen is the one that can eradicate H. pylori infection in more than 90% of cases. Graham classified the efficacy of treatment according to per protocol success as A: excellent (>95% eradication rate), B: good (90-95%), C: fair (85-89%), D: poor (81-84%) and F: unacceptable (<80%).[30]

CONCLUSIONS

According to above descriptions, the results of our study show that the eradication regimen used for group B (omeprazole tablets 20 mg, amoxicillin capsules 1gr, bismuth subcitrate tablets 240 mg twice daily for two weeks and furazolidone tablets200 mg twice daily just during the first week), with 90.27% per-protocol eradication rate, can be an ideal regimen for H. pylori eradication in Iran.

REFERENCES

1. Egan BJ, Marzio L, O'Connor H, O'Morain C. Treatment of Helicobacter pylori infection. Helicobacter 2008;13(Suppl. 1):35–40.
2. Ernst PB, Crowe SE, Reyes VE. How does Helicobacter pylori cause mucosal damage? The in-amatory response. Gastroenterology 1997;113(suppl 6):S35–S42; discussion S50.
3. Peura DA. Helicobacter pylori and ulcerogenesis. Am J Med 1996;100:19S–25S; discussion S-6S.
4. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, et al. Helicobacter pylori infection and gastric lymphoma. N Engl J Med 1994;330:1267–1271.
5. Alexander GA, Brawley OW. Association of Helicobacter pylori infection with gastric cancer. Mil Med 2000;165:21–27.
6. European Helicobacter Pylori Study Group. Current European concepts in the management of Helicobacter pylori infection. The Maastricht Consensus Report.Gut 1997;41:8–13.
7. Chey WD, Wong BCY. Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol 2007;102:1808-1825.
8. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III consensus report. Gut 2007;56:772-781.
9. Kaviani MJ, Malekzadeh R, Vahedi H, Sotoudeh M, Kamalian N, Amini M, et al. Various duration of a standard regimen (amoxicillin, metronidazole, colloidal bismuth subcitrate for 2 weeks or with additional ranitidine for 1 or 2 weeks on eradication of Helicobacter pylori in Iranian peptic ulcer patients. A randomized controlled trial. Eur J GastroenterolHepatol 2001;13:915–919.
10. Salman-Roghani H, Massarrat S, Pahlewanzadeh MR, Dashti M. Effect of two doses of metronidazole and tetracycline in bismuth triple therapy on eradication of H.pylori and its resistant strains. Eur J GastroenterolHepatol 1999;11:709–712.
11. 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 GastroenterolHepatol 1995;7(5):427–433.
12. Siavoshi F, Saniee P, Lati-Navid S, Massarrat S, Sheykholeslami A. Increase in Resistance Rates of H.pylori Isolates to Metronidazole and Tetracycline-Comparisonof Three 3-Year Studies Archives of Iranian Medicine, 2010;13(3).
13. Fakheri H, Malekzadeh R, Merat S, Khatibian M, Fazel A, Alizadeh BZ, et al. Clarithromycin vs. furazolidone in quadruple therapy regimens for the treatment of Helicobacter pylori in a population with a high metronidazole resistance rate.Aliment Pharmacol Ther 2001;15(3):411-416.

14. Fakheri H, Merat S, Hosseini V, Malekzadeh R. Low-dose furazolidone in triple and quadruple regimens for Helicobacter pylori eradication.Aliment PharmacolTher 2004;19(1):89-93.
15. Saberi-Firoozi M, Massarrat S, Zare S, Fattahi M, Javan A, Etaati H, et al. Effect of triple therapy or amoxicillin plus omeprazole or amoxicillin plus tinidazole plus omeprazole on duodenal ulcer healing, eradication of Helicobacter pylori, and prevention of ulcer relapse over a 1-year follow-up period: A prospective, randomized, controlled study. Am J Gastroenterol 1995;90:1419-1423.
16. Fischbach LA, Goodman KJ, Feldman M, Aragaki C. Sources of variation of Helicobacter pylori treatment success in adults worldwide: A meta-analysis. Int J Epidemiol 2002;31:128-139.
17. Vakil N. Are there geographical and regional differences in Helicobacter pylori eradication? Can J Gastroenterol 2003;17(Suppl. B):30B–32B.
18. Altamirano A, Bondani A. Adverse reactions to furazolidone and other drugs. A comparative review. Scand J Gastroenterol Suppl. 1989;169:70–80. [PubMed]
19. Kwon DH, Lee M, Kim JJ, Kim JG, El-Zaatari FA, Osato MS, et al. urazolidone- and nitrofurantoin-resistant Helicobacter pylori: prevalence and role of genes involved in metronidazole resistance. Antimicrob Agents Chemother 2001;45:306–308.
20. Graham DY, Osato MS, Hoffman J, Opekun AR, Anderson SY, El-Zimaity HM. Furazolidone combination therapies for Helicobacter pylori infection in the United States.Aliment PharmacolTher 2000;14(2):211-215.
21. Daghaghzadeh H, Emami MH, Karimi S, Raeisi M. One-week versus two-week furazolidone-based quadruple therapy as the first-line treatment for Helicobacter pylori infection in Iran.J GastroenterolHepatol 2007;22(9):1399-1403.
22. Felga GE, Silva FM, Barbuti RC, Navarro-Rodriguez T, Zaterka S, Eisig JN. Quadruple therapy with furazolidone for retreatment in patients with peptic ulcer disease.World J Gastroenterol 2008;14(40):6224-6227.
23. Cheng H, Hu FL. Furazolidone, amoxicillin, bismuth and rabeprazole quadruple rescue therapy for the eradication of Helicobacter pylori.World J Gastroenterol 2009;15(7):860-864.
24. Sanches B, Coelho L, Moretzsohn L, Vieira G. Failure of Helicobacter pylori treatment after regimes containing clarithromycin: New practical therapeutic options.JrHelicobacter 2008;13(6):572-576.
25. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance.Gut 2010;59(8):1143-1153. Epub 2010 Jun 4
26. 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 multicenter, randomized, double-blind study. Aliment PharmacolTher 2001;15:1975–1979.
27. Liu WZ, Xiao SD, Hu PJ, Lu H, Cui Y, Tytgat GN. A new quadruple therapy for Helicobacter pylori using tripotassiumdicitratobismuthate, furazolidone, josamycin, and famotidine. Aliment PharmacolTher 2000;14:1519–1522.
28. 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):161-167.
29. Hasan SR, Vahid V, Reza PM, Roham SR. Short-duration furazolidone therapy in combination with amoxicillin, bismuth subcitrate, and omeprazole for eradication of Helicobacter pylori.Saudi J Gastroenterol 2010;16(1):14-18.
30. Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. Helicobacter. 2007; 12:275–278.

Authors Contribution:

Hafez Tirgar Fakheri: Designed and conducted the study besides literature search, analysis and interpretation of data.
Moloud Fakhri: Drafted and Reviewed the manuscript.
Soheila Shahmohammadi: Helped in translation and literature search.