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Furazolidone, amoxicillin and omeprazole with or without bismuth for eradication of *Helicobacter pylori* in peptic ulcer disease

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Background/aims: *Furazolidone has been introduced as an effective drug against Helicobacter pylori infection in Iran, but intolerable side effects may limit its use. The aim of this study was to compare quadruple and triple furazolidone-based regimens to achieve an economically affordable regimen with acceptable success rate and fewer side effects.* ***Methods:*** *Patients with Helicobacter pylori positive peptic ulcer disease were randomly allocated into two groups: amoxicillin 1 g b.i.d., furazolidone 200 mg b.i.d. and omeprazole 20 mg b.i.d. with or without bismuth subcitrate 240 mg b.i.d. for two weeks (amoxicillin, furazolidone, omeprazole, bismuth and amoxicillin, furazolidone, omeprazole regimens, respectively). Helicobacter pylori eradication was confirmed by ^{13}C-urea breath test 12 weeks after the end of therapy.* ***Results:*** *Eighty-six patients were enrolled, but 16 patients discontinued their therapy or follow-up. The eradication rates with amoxicillin, furazolidone, omeprazole, bismuth and amoxicillin, furazolidone, omeprazole were 85.3% and 61.1% by per-protocol analysis, respectively (p=0.02) and 67.4% and 51.2% by intention–to-treat analysis, respectively (p<0.05). The most frequent adverse effects in the two study groups were weakness, nausea, anorexia, and dizziness, and no significant differences between the groups were shown.* ***Conclusions:*** *Based on the results in this study, furazolidone-based triple therapy (without bismuth) is not recommended for Helicobacter pylori eradication because of the lower eradication rate and unchanged frequency of adverse effects. Thus, we recommend furazolidone, amoxicillin and omeprazole in combination with bismuth for treatment of Helicobacter pylori.*

Key words: Duodenal ulcer, gastric ulcer, *Helicobacter pylori,* eradication, triple therapy, quadruple therapy

Peptik ülser hastalığında *Helikobakter pilori* eradikasyonunda furazolidon, amoksisillin, omeprazol ile birlikte bizmut tedavisi

Amaç: *Furazolidon, Helikobakter pilori enfeksiyonuna karşı etkin bir ilaç olarak İran'da sunulmaktadır, ancak tolere edilemeyen yan etkileri kullanımını kısıtlamaktadır. Bu çalışmanın amacı furazolidon tabanlı dörtlü ve üçlü tedavi rejimleri karşılaştırmak ve kabul edilebilir başarı oranı ve daha az yan etkisi olan ekonomik bir tedavi rejimini tespit etmektir.* ***Yöntem:*** *Helikobakter pilori pozitif peptik ülser hastalığı olan hastalar iki gruba randomize edildi. İki hafta süre ile amoksisillin 1 gr (2x1), furazolidon 200 mg (2x1) ve omeprazol 20 mg (2x1) +/- Bizmut subsitrat 240 mg (2x1) (Sırasıyla, amoksisilin, furazolidon, omeprazol, bizmut ve amoksisilin, furazolidon, omeprazol rejimleri). Helikobakter pilori eradikasyonu tedavi bitiminden 12 hafta sonra ^{13}C-üre nefes testi ile kontrol edildi.* ***Bulgular:*** *Çalışmaya 86 hasta katıldı, ancak 16 hasta tedaviyi tamamlamadı veya takibe gelmedi. amoksisillin, furazolidon, omeprazol, bizmut ve amoksisilin, furazolidon, omeprazol tedavilerinin eradikasyon oranları tedaviyi bitiren hastaların (per-protokol) analizinde sırasıyla %85, 3 ve %61,1 (p=0.02) ve tedaviye başlayan hastaların (intention-to-treat) analizinde sırasıyla %67,4 ve %51,2 bulundu (p<0.05). Her iki çalışma grubunda en sık karşılaşılan yan etkiler halsizlik, bulantı, iştahsızlık ve baş dönmesi olarak tespit edildi ve gruplar arası benzer bulundu.* ***Tartışma:*** *Bu çalışmanın sonuçlarına göre, furazolidon tabanlı tedavi (bizmut eklenmeden) Helikobakter pilori eradikasyonu için, düşük eradikasyon oranı ve karşılaşılan yan etkiler nedeni ile tavsiye edilmemektedir. Sonuç olarak, furazolidon, amoksisilin ve omeprazol ile bizmut'un birlikte kullanılmasını Helikobakter pilori tedavisinde önermekteyiz.*

Anahtar kelimeler: Duodenal ülser, Helikobakter pilori, eradikasyon, üçlü tedavi, dörtlü tedavi

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INTRODUCTION

The discovery of *Helicobacter pylori (H. pylori)* as a causative agent of peptic ulcer disease (PUD) has revolutionized the medical field's understanding of the treatment of this condition (1). *H. pylori* plays an integral role in the pathogenesis of PUD, and its successful eradication substantially reduces the risk of ulcer recurrence and rebleeding (2,3). Consequently, there has been great emphasis placed on the successful eradication of this infection. Multiple first-line treatments have been employed, and the most successful regimens achieve eradication rates ranging from 75 to 92% (4). Seroepidemiologic studies in different parts of Iran revealed a near 90% prevalence of *H. pylori* infection in adults older than 35 years (5). Clinical experience in our country has demonstrated that the eradication rate of *H. pylori* is much lower than the rate reported from western and developed countries, and a high rate of metronidazole resistance (37%) and an increasing rate of resistance to clarithromycin have emerged (6). Thus, the treatment regimens suggested in studies from the western world may not be ideal in Iran, and treatment regimens and the duration of treatment should be defined on the basis of local surveys. These regimens must be effective, safe and economically affordable, with minimal induction of resistance.

According to recent studies from our country, furazolidone may be used as an alternative to metronidazole (7,8). Furazolidone offer the advantage of low cost, but unfortunately, more adverse effects influence the drug efficacy (9,10). It should be considered that triple therapy with amoxicillin, furazolidone and omeprazole (AFO) is more tolerable due to fewer required drugs and is more economically affordable. In this study, we compared a two-week AFO regimen with bismuth added to same regimen (AFOB) with respect to their efficacy and side effects.

MATERIALS AND METHODS

Consenting patients, 18 years or older, with endoscopically proven gastric or duodenal ulcers who attended the outpatient gastrointestinal clinics in Qum, Iran were enrolled. *H. pylori* infection was proven either by a positive rapid urease test or by histopathological examination.

Patients were excluded if they were pregnant; glucose-6 phosphate dehydrogenase (G_6PD)-deficient; if they had a history of chronic kidney, liver or lung failure, previous gastrointestinal (GI) surgery, or recent upper GI bleeding; if they had used non-steroidal anti-inflammatory drug (NSAID) or antibiotic in the past four weeks; or if they had any known allergic reaction to drugs used in the treatment regimens. We also excluded patients who were currently breast-feeding. Patients were randomized (computer-generated block randomization) to receive one of the two anti *H. pylori* regimens.

The AFOB group received amoxicillin 1 g/BID, furazolidone 200 mg/BID, omeprazole 20 mg/BID, and bismuth subcitrate 240 mg/BID for two weeks. The AFO group received amoxicillin 1 g/BID, furazolidone 200 mg/BID, omeprazole 20 mg/BID, and placebo two times a day for two weeks. Each drug package was identified by a code and the codes were broken at the end of the study.

The patients were instructed about the use of the medications and probable side effects and were advised to contact us in the event of any problematic adverse effects. We also checked the patients' compliance by pill counting and recorded any adverse events or newly started medications other than the study medications. Acceptable compliance was defined when the patients took at least 80% of the given drugs.

We performed a ^{13}C-urea breath test (UBT) 12 weeks after completing the treatment. Seventy-five mg of ^{13}C-urea was given in a fasting state. The ^{13}C in the expired air was measured 20 minutes later, using an infrared spectrophotometer (IRIS, Dr. Wagner, Bremen, Germany). The cut-off value for negative UBT was less than 2.5 (delta over base) according to a previous study (11). We used chi-square and Student-t tests for statistical analysis. A p-value less than 0.05 was considered significant ($p<0.05$, two-sided).

RESULTS

Eighty-six patients were enrolled. Sixteen patients were lost to follow-up and 70 patients were followed at the second week. The baseline characteristics of the patients are shown in Table 1.

Out of 16 patients who discontinued the follow-up, 6 patients (3 in each study group) showed adverse drug effects that were considered intolerable. Four patients were noncompliant (see the Methods section) and 6 patients did not participate in the UBT; thus, these 16 patients were not included in the per-protocol analysis. At the end of the study,

Table 1. Characteristics of the patients in the two groups

Characteristics	AFOB	AFO	P-value
Mean age (year)	41.38±2.21	41.25±2.37	NS
Gender ($\frac{M}{F}$) n	($\frac{19}{15}$)	($\frac{14}{22}$)	NS
Current smokers	9 (26.4%)	10 (27.7%)	NS
History of GI bleeding	13 (38.2%)	12 (33.3%)	NS
History of NSAID use	10 (29.4)%	9 (25%)	NS
Ulcer size ≥10 mm	14 (41.2%)	16 (44.4%)	NS
Number of patients	34	36	

NS: Not significant.
NSAID: Non-steroidal antiinflammatory drug

36 patients in the AFO group and 34 patients in the AFOB group were included. Successful eradication in the two groups is shown in Table 2.

The reported adverse effects are shown in Table 3.

DISCUSSION

Furazolidone-based combination therapy produced eradication rates around 80% in different studies (8,12,13). Despite this advantage, adverse reactions to furazolidone, which usually occurred in the second week of treatment and led to interruption of the treatment in many instances, limit its use (11,14). Compliance with any medical therapy is influenced by the complexity of the dosing regimen (number of pills and frequency) and also the frequency and severity of associated side effects. Unfortunately, disadvantages of bismuth-based quadruple therapy include the large daily pill count (potentially exceeding 14 pills), dosing frequency (occasionally four times daily) and frequent side effects, occurring in >50% of patients in some studies (15-17). On the other hand, 9% of patients receiving the quadruple regimen including bismuth salts (subcitrate and subsalicylate) had very high blood bismuth concentration within the Hillemand "alarm level" (18). Nitrofuran-based regimens had an acceptably high eradication rate (>85%) in first-line therapy by using a quadruple combination with proton pump inhibitor (PPI), bismuth salts, amoxicillin, and either furazolidone or nifuratel (19). In our study, eradication rates with AFOB and AFO regimens were 85.3% and 61.1%, respectively (p=0.02). In another study from Iran, these eradication rates were 72% and 54%, respectively (p<0.01) (14); thus, bismuth added to AFO significantly increased the rate of eradication. In our study, there were no significant differences in side effects between the AFOB and AFO groups. Fakheri et al. (14) showed that the frequency of side effects in the AFO group was less than in the AFOB group (32% versus 62%, respectively). In that study, the low dose of furazolidone used was different from our study. Roghani et al. (9) showed that furazolidone in combination with amoxicillin and omeprazole should be used as a higher dose. They concluded that, although serious adverse effects were less frequent with the low-dose regimen, the intention-to-treat eradication rate was not acceptable. In one study from Hong Kong, a low dose of furazolidone (100 mg BID) was used in patients failing standard *H. pylori* eradication. An eradication rate close to 50% was observed (20). Although this rate may be acceptable for rescue therapy, it is unacceptable for primary treatment. Unfortunately, we did not perform antibiotic susceptibility testing, but according to another study from our country, we conclude that low-dose furazolidone would not be an ideal option for H. pylori eradication and should not be recommended in developing countries with high resistance to metronidazole.

On the other hand, a good *H. pylori* eradication regimen should reach the eradication rate of intention-to-treat >80% and per protocol >90% (21). In consideration of the high resistance rate to antibiotics, a per protocol eradication rate of 85.3% with the AFOB regimen should be accepted and the 61.1% with the AFO regimen should not be considered acceptable; thus, we conclude that quadruple therapy including furazolidone is superior to its use in triple therapy.

Table 2. Comparison of the eradication rate in the two study groups

Eradication rate	AFOB	AFO	P-value
Per-protocol analysis (n=70)	85.3% (95% CI=73.3-97.3%) (n=34)	61.1% (95% CI=45.2-77%) (n=36)	0.02
Intention-to-treat analysis (n=86)	67.4% (95% CI=53.4-81.4%) (n=43)	51.2% (95% CI=36.3-66.1%) (n=43)	<0.05

CI: Confidence interval.

Table 3. Reported adverse effects in the study groups

Adverse effect	AFOB n (%)	AFO n (%)	P-value
Weakness	28 (82.3%)	23 (63.8%)	NS
Nausea	11 (32.3%)	11 (30.5%)	NS
Anorexia	11 (32.3%)	7 (19.4%)	NS
Dizziness	8 (23.5%)	13 (36.1%)	NS
Pyrosis	7 (20.5%)	7 (19.4%)	NS
Headache	6 (17.6%)	6 (16.6%)	NS
Constipation	5 (14.7%)	7 (19.4%)	NS
Dry mouth	4 (11.7%)	6 (16.6%)	NS
Diarrhea	3 (8.8%)	2 (5.5%)	NS
Bloating	2 (5.8%)	4 (11.1%)	NS
Palpitation	2 (5.8%)	3 (8.3%)	NS
Vomiting	1 (2.9%)	0 (0%)	NS
Dyspnea	1 (2.9%)	1 (2.7%)	NS
Pruritus	0 (0%)	2 (5.5%)	NS

NS: Not significant.

In our study, 7% of the patients in the two study groups had adverse drug reactions that required drug discontinuation. In another previous study from our center, only 2 patients out of 54 (3.7%) who were treated with furazolidone-based triple therapy could not tolerate the medication (22). Similarly, Fakheri et al. (14) reported that the number of patients who discontinued treatment with a furazolidone-containing regimen was not significant, and the severe adverse effect rate in the AFO regimen was reported as 8% ($\frac{4}{50}$).

The side effects of furazolidone are frequent but mild and well tolerated by most patients. We concluded that patients need more time to learn our recommendations; telephone interview may be a good means of communication to decrease their anxiety about the drug side effects. The patients should be educated regarding the importance of *H. pylori* eradication to increase treatment compliance. Primary and acquired bacterial resistance against different antibiotics has been clearly demonstrated and has increased in the last decade (23). Efficacy of first-line therapy is of paramount importance; "rescue" treatments are generally more expensive and less effective. Thus, we should use regimens with high efficacy, with proper dose and duration. Bismuth salts act by detaching the organism from the mucosa and causing their lyses. These compounds have been generally used as first-line regimens (23). In our study, bismuth salts had a significant role against *H. pylori*. According to this study, furazolidone-based quadruple therapy including bismuth salts was preferred to triple therapy, and the frequency of important side effects was not significantly higher in the "quadruple" regimen group.

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