Helicobacter pylori infection plays an important role in the pathogenesis of peptic ulcer disease. Its eradication leads to cure of the disease and prevents relapse.\cite{1,2} The optimal regimen should have high efficacy, tolerable side effects, simple dosage and should be economical. Intensive efforts are being made to identify such an optimal regimen, but there are many obstacles hindering the achievement of this goal. The H pylori strains have high diversity, with resistance to antibiotics varying in the different regions in the world.\cite{3,4} The number of strains of H pylori that are resistant to metronidazole and clarithromycin has been increasing during the past few years. Clinical experience shows that regimens recommended for H pylori eradication in developed countries do not show the same efficacy in developing countries.\cite{5,6,7} In Iran, many strains of H pylori are resistant to metronidazole and clarithromycin but not to furazolidone.\cite{8,9} Furazolidone is an effective antibiotic against H pylori infection but its serious (though rare) adverse effects at the therapeutic dose (400 mg/day) limits its widespread use.\cite{10} The sensitivity of H pylori to metronidazole and clarithromycin can increase the efficacy of furazolidone.\cite{11}

In our previous study, we observed that there is significant increase in the efficacy of furazolidone in H pylori eradication when the dose is increased from 100 mg to 400 mg a day; however, the side effects also increase.\cite{12} Although previous studies in Iran have shown that metronidazole could be replaced with furazolidone,\cite{6,7,13} a 2-week course of furazolidone at 400 mg/day is associated with significant side effects; unfortunately, eradication cannot generally be achieved with a dose under 400 mg/day.\cite{14} In addition, reports from Iran have also shown that a period of treatment of less than 14 days reduces the chances of cure.\cite{10,11} So, the aim of present study was to assess the cure rate and side effects of a 1-week course of furazolidone (400 mg/day) given in combination with 2 weeks of bismuth subcitrate,
amoxicillin, and omeprazole. Additionally, in one group of patients, metronidazole was added in the second week of the treatment period to find out how this affected the rate of *H pylori* eradication.

**PATIENTS AND METHODS**

A total of 177 patients with *H pylori*-associated duodenal ulcer, proven by endoscopic findings, were enrolled in this study. The exclusion criteria were as follows: Age <15 years; gravidity or lactation; glucose-6-phosphate dehydrogenase deficiency (which is common in this region); history of gastric surgery; history of upper gastrointestinal bleeding in the last 4 weeks; intake of antibiotics or any acid suppressant or nonsteroidal anti-inflammatory drugs in the preceding 4 weeks; history of drug allergy; presence of chronic hepatic, renal, or pulmonary disease; contraindication to any of the drugs used in the study; and history of having undergone eradication therapy in the past.

The aim and nature of the trial was fully explained to the patients and their consent obtained. The enrolled patients were randomly allotted into two groups to receive the following medications:

- **Group I:** Omeprazole (capsules, 20 mg) b.i.d (before breakfast and dinner), amoxicillin (capsules, 1 g) b.i.d (with breakfast and dinner), bismuth subcitrate (tablets, 120 mg) q.i.d for 2 weeks, and furazolidone (tablets, 200 mg) b.i.d (with breakfast and dinner) for 1 week.
- **Group II:** Received the same regimen as group I, except that in the second week metronidazole (tablets, 500 mg) b.i.d. was given instead of furazolidone (i.e., 1 week furazolidone and 1 week metronidazole).

Subjects were questioned 2 weeks post treatment regarding any adverse effects and drug compliance. Use of more than 80% of the recommended drugs was considered as good compliance. Control endoscopy was done 8 weeks after completion of treatment, and three specimens were taken from the antrum and three from the corpus for rapid urease test and histologic examination.

Hematoxylin-cosin, Alcian blue, and Giemsa stains were used for morphologic examination of helicobacter-like organisms (HLO) and the updated Sydney system was used for grading. Histopathology was performed by a specialized pathologist. Eradication was assumed if all six specimens were negative for *H pylori*.

**Statistical analysis**

Statistical calculations were performed with SPSS, version 10.0 (SPSS Inc., Chicago, IL., USA). Demographic characteristics, *H pylori* cure rates, and side effects were compared using the two-tailed Pearson chi-square test. All patients were evaluated in an ITT analysis, in which patients without final *H pylori* determination or with protocol violation were considered treatment failures. The PP analysis included all subjects who took at least 80% of each study medication as prescribed and who completed the final *H pylori* status assessment. Statistical significance was set at *P* < 0.05.

**RESULTS**

Of 177 patients who were enrolled, 157 patients completed the study; 55.4% were males and 44.6% were females. The mean age was 38.84 ± 10.42 years (range: 14-80 years). There were no significant differences between the two groups with regard to age, gender, smoking habits, and endoscopic findings [Table 1].

Only two patients from group I and three from group II did not tolerate the regimen; these patients were excluded from the study [Table 2]. There were no serious complications. Thus, decreasing the duration of furazolidone treatment to 1 week with a dose of 400 mg/day was not associated with

| Table 1: Patient demographics and clinical characteristics |
|----------------------------------------------------------|
| Group I *(n = 92)*                                      | Group II *(n = 85)* | Significance |
| Male/female ratio                                       | 53/39               | 45/40        | 0.71         |
| Mean age (years ± SD)                                   | 37.01 ± 8.7         | 39.83 ± 10.73| 0.56         |
| Mean duration of ulcers (years ± SD)                    | 7.34 ± 2.5          | 1.23 ± 2.8   | 0.88         |
| Mean replace rate in last 2 years (n ± SD)              | 2.84 ± 0.84         | 2.7 ± 0.94   | 0.92         |
| Mean length of present pain period (weeks ± SD)        | 6.31 ± 1.81         | 6.35 ± 1.71  | 0.89         |
| Smoker [%]                                              | 15.9%               | 16.2        | 0.84         |
| Endoscopy findings                                      | 1.45 ± 4            | 1.53 ± 5    | 0.98         |
| Mean number of ulcers                                   | 11.5 ± 1.8          | 11.3 ± 1.8  | 0.84         |
| Mean ulcer diameter (mm ± SD)                           | 90/2                | 84/1        | 0.96         |

1No significant difference between the two groups. Patient compliance, measured by returned-pill count, was considered good (more than 80% of prescribed) for both treatment regimens. Both therapies were well tolerated by patients. Although some patients in both groups experienced some degree of side effects [Table 2], none of the side effects were considered clinically serious, and all but five patients completed the course of treatment. Two (2.1%) patients in group I and three (3.5%) in group II reported side effects that interfered with their normal activities on day 4-6 post treatment; the side effects included fever, nausea, weakness, and vomiting. Eight patients (8.7%) from group I and seven (8.2%) from group II failed to return for follow-up investigations (control endoscopy) and were excluded. Thus, 82 (89.1%) of the 92 patients in group I and 76 (89.2%) of the 85 patients in group II successfully completed the study [Table 3]. Eradication results are shown in Table 4. Eradication rate by ITT analysis was 79.3% in group I and 76.4% in group II (*P* = 0.32). Eradication rate by PP analysis was 89% in group I and 86.6% in group II (*P* = 0.33).
severe adverse effects.

There was no significant difference between the eradication rates in the two groups both by PP and ITT analysis. The addition of metronidazole in the second week of treatment did not result in an increase in the eradication rate, but it was associated with more side effects [Tables 3 and 4].

**DISCUSSION**

The eradication rate of *H pylori* infection in peptic ulcer patients in developing countries is far from optimal with the recommended regimens from developed countries. About 40-70% of *H pylori* strains are resistant to metronidazole, which is believed to be the main cause of treatment failure. The increase in the prevalence of resistant strains observed in developing countries, as well as in European countries and North America, is the reason for the poor efficacy of metronidazole-based regimens.

Clarithromycin, a macrolide antibiotic, has been used and recommended in the European and North American consensus conferences as an effective drug to replace metronidazole. However, this drug is not a feasible option in developing countries because of its high cost. Reports about the development of strains resistant to this drug are also increasing. O’Morain et al. reported an increase in the prevalence of resistant strains from 1% to 13%. Graham et al. has described the problems faced when treating clarithromycin-resistant strains of *H pylori*. The results obtained with various regimens in Iran reveal the presence of special and more toxic strains that do not respond to the optimal regimens recommended in developed countries. This is a challenging situation for developing countries, necessitating the use of a new drug in place of clarithromycin.

Furazolidone is an antibiotic that was introduced in the late 1950s. It is effective against both gram-negative and gram-positive bacteria. It has good enteral absorption as well as tissue distribution. It has an ability to promote peptic ulcer healing, which is now known to be via its action on *H pylori*.

In the past few years, there have been many reports about the efficacy of furazolidone when used in combination regimens, and many authors have considered this drug as a good replacement for clarithromycin. The sensitivity of *H pylori* to furazolidone is reported to be very high in South Korea. In various reports, fewer than 4% of strains were found to be resistant to furazolidone. In Iran, where the *H pylori* strains have been shown to be resistant to metronidazole in 37-40% of cases and against clarithromycin in 15% of cases, none of these factors were resistant to furazolidone. Its monoaminoxidase-inhibitor effect causes these side effects, which can probably be prevented by avoiding tyramine-containing foods such as old cheese. Our previous study revealed that most of the serious side effects with a dose of 400 mg/day occur...

### Table 2: Adverse treatment effects

| Side Effect          | Group I (n) | Group II (n) | Significance (P) |
|----------------------|-------------|--------------|------------------|
| Fever                | 2           | 1            |                  |
| Fatigue              | 2           | 2            |                  |
| Dizziness            | 3           | 3            |                  |
| Headache             | 2           | 4            |                  |
| Nausea               | 3           | 5            |                  |
| Diarrhea             | 5           | 4            |                  |
| Rash                 | 3           | 3            |                  |
| Urticaria            | 1           | 2            |                  |
| Vomiting             | 1           | 1            |                  |
| Anorexia             | 1           | 6*           |                  |
| Taste disturbance    | 1           | 7**          |                  |
| Dark stool           | 15          | 14           |                  |
| Total [n (%)]        | 39 (47.6)   | 52 (69.3)    |                  |

*P = 0.016; **P = 0.001

### Table 3: Overview of treatment results

| Parameter                        | Group I [n (%)] | Group II [n (%)] | Significance (P) |
|----------------------------------|-----------------|------------------|------------------|
| Number of patients               | 92 (100)        | 85 (100)         | -                |
| Good compliance (i.e., > 80% drug taken) | 79 (96.4)      | 67 (89.2)        | 0.71             |
| Therapy discontinued because of drug’s side effects | 2 (2.1)         | 3 (3.5)          | 0.59             |
| Lost to follow-up at 6 weeks     | 8 (8.7)         | 7 (8.2)          | 0.69             |
| Patients who completed the study at 6 weeks | 82 (89.1)     | 75 (88.2)        | 0.96             |
| Ulcer healing rate               | 77/82 (93.9)    | 71/75 (94.6)     | 0.49             |

### Table 4: Comparison of eradication between the two groups

| Parameter                        | Group I [n (%)] | Group II [n (%)] | Significance (P) |
|----------------------------------|-----------------|------------------|------------------|
| Per-protocol analysis [n (%)]    | 73/82 (89)      | 65/75 (86.6)     | 0.33*            |
| 95% CI                           | (82 to 96)      | (79 to 95)       |                  |
| Intention-to-treat analysis [n (%)] | 73/92 (79.3)   | 65/85 (76.4)     | 0.32*            |
| 95% CI                           | (71 to 87)      | (67 to 85)       |                  |

*There was no significant difference between the two groups. CI: Confidence interval
in the second half of the therapy period, 10 days after the beginning of drug therapy.[14]

Microbiological investigations have also revealed that low concentrations of furazolidone in medium (5 mg/cc) can suppress the growth of H pylori, without development of drug resistance. Thus, dose adjustment and reduction in the duration of treatment appear to be reasonable approaches.[41]

In our previous study, we observed a significant decrease in both side effects and efficacy of furazolidone (in the eradication of H pylori) when the dose was lowered from 400 mg to 100 mg.[14] Fakheri et al. has reported similar results.[41] Thus, a shorter period of treatment with furazolidone and the addition of another drug (such as bismuth), in combination with amoxicillin and omeprazole, seems to be reasonable.[44]

Studies from developing countries such as Iran have shown that regimens shorter than 2 weeks were not as effective as they were reported to be in the developed countries.[10] Our previous study found that furazolidone at a dose of 400 mg daily for more than 1 week led to severe adverse effects.[14] In the present study we advised furazolidone for only 1 week in order to decrease the drug’s side effects. We found that this improved compliance.

Xiao et al. treated patients with furazolidone in combination with amoxicillin and omeprazole for 1 week and found a high eradication rate of 86% and 87% by ITT and PP analysis, respectively.[38] In another study, furazolidone was given (in combination with amoxicillin and metronidazole) only for 5 days but at a high dose of 600 mg daily, and the authors reported that serious complications were not seen. The eradication rate did not differ when the duration of therapy was prolonged to 10 days.[34]

Another aspect of therapy is the improvement in efficacy seen when bismuth is given in combination with furazolidone plus amoxicillin and omeprazole for H pylori eradication.[44] In the present study we decided not only to reduce the duration of treatment with furazolidone but also to add bismuth subcitrate to the regimen.

De Boer et al. has reported that metronidazole administered at a dose of over 750 mg per day could overcome bacterial resistance.[44] Therefore, in the present study, after 1 week of furazolidone therapy we administered 1000 mg/day of metronidazole in group II.

CONCLUSION

This study showed that, as compared with clarithromycin-containing regimens, 400 mg/day of furazolidone for 1 week given in combination with 2 weeks of amoxicillin, omeprazole, and bismuth subcitrate is a good, safe, and cost-effective regimen for the eradication of H pylori in Iran. There are few side effects with this regimen and therefore patient compliance is very good. The addition of metronidazole in the second week of the treatment period does not appear to increase the eradication rate.

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Source of Support: Nil, Conflict of Interest: None declared.