

Original Article

Furazolidone-Based, Metronidazole-Based, or a Combination Regimen for Eradication of *Helicobacter pylori* in Peptic Ulcer Disease

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Background: Furazolidone has been effective against *Helicobacter pylori* in Iran, with no resistance, but with intolerable side effects in the second week. One-week regimens have not been useful here. We compared the efficacy and side effect profiles of three anti-*H.pylori* regimens.

Methods: Patients with peptic ulcer disease and positive *H.pylori* infection were randomly allocated into three groups. The patients in group A received omeprazole 20 mg + amoxicillin 1g + metronidazole 500 mg, and bismuth subcitrate 240 mg twice daily each, for two weeks; the patients in group B received the same regimen but metronidazole was replaced by furazolidone 200 mg twice daily; and the patients in group C received regimen B for the first week and regimen A for the second week. *H.pylori* eradication was verified with ¹³C- urea breath test at the tenth week.

Results: Three hundred and fourteen patients were enrolled; 107, 104, and 103 patients in groups A-C, respectively but 278 patients completed the study. Seven, three, and six patients discontinued their medication in groups A-C, respectively. Fever, dizziness, and weakness were more common in group B than group C ($P < 0.05$). Vomiting, pruritus, and rash were more common in group C than group A ($P < 0.05$). Per-protocol eradication rates were 83.1%, 95.2%, and 95.3% in groups A-C, respectively ($P = 0.005$, groups A and C). Intention to treat eradication rates were 74.5%, 87.0%, and 86.6% in groups A-C, respectively ($P = 0.02$, groups A and C).

Conclusion: One-week furazolidone followed by one-week metronidazole regimen is as efficient as two-week furazolidone regimen but with fewer side effects. Furazolidone-based regimens are superior to metronidazole-based ones for *H.pylori* eradication in Iran.

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Keywords: Duodenal ulcer • eradication • gastric ulcer • *H.pylori*

Introduction

Therapeutic regimens for *Helicobacter pylori* eradication must be effective, safe, and economically affordable with minimal induction of resistance. For more than two decades that the effectiveness of combination therapy has been established, but no single regimen

has yet achieved near 100% eradication rate.

Currently, there are two regimens most commonly recommended: 1) triple therapy with omeprazole, clarithromycin, and either amoxicillin or metronidazole and 2) quadruple therapy with a bismuth derivative, metronidazole, tetracycline, and an acid-suppressing drug.¹⁻⁴ Both of these regimens are used for one to two weeks.

In Asian countries, *H.pylori* eradication is more problematic and generally two weeks of treatment is necessary.⁵⁻⁸ Metronidazole resistance is a serious problem and clarithromycin is rather expensive especially if prescribed for two weeks.^{8,9} Furazolidone had been used for the treatment of peptic ulcer disease (PUD) and

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prevention of ulcer relapse in China, long before the infectious basis for PUD was known.¹⁰ Few studies showed that furazolidone was an effective anti-*H.pylori* antibiotic.^{11, 12, 13} *H.pylori* is sensitive to furazolidone and reports of resistance have been scarce so far.^{9, 14, 15} We had previously shown that furazolidone was effective against *H.pylori* in Iranian patients and was a good substitute for clarithromycin or metronidazole.¹⁶⁻¹⁸

Furazolidone consumption for two weeks, however, is associated with intolerable adverse reactions such as anorexia, dizziness, urticarial rash, flu-like symptoms, and fever in 5 – 15% of cases, therefore, hindering its excellent anti-*H.pylori* effect.^{8, 16} In addition to its efficacy, furazolidone is a relatively inexpensive and easily affordable medication. As the side effects usually appear in the second week of treatment, we designed this study to assess the efficacy and tolerability of a two-week furazolidone-based regimen with that of a two-week metronidazole-based regimen and a combination one, in which furazolidone and metronidazole were administered for one week each in sequence.

Materials and Methods

Consenting patients, 18 years or older, with endoscopically-proven duodenal ulcer, gastric ulcer, or erosive duodenitis who attended to ten outpatient gastrointestinal (GI) clinics in Tehran, Iran were enrolled. *H.pylori* infection was proved either by a positive rapid urease test or by histopathological examination. Patients were excluded if they were pregnant, were nursing a baby, had a history of gastric surgery, had taken antibiotics within the past month, or had allergy to any of the study drugs. They were randomized (computer-generated, block randomization) to receive one of the three anti-*H.pylori* regimens.

The first group received omeprazole 2x20 mg, bismuth subcitrate 2x240 mg, amoxicillin 2x1 g, and metronidazole 2x500 mg per day for two weeks (regimen A). The second group received the same treatment but metronidazole was replaced by furazolidone 2x200 mg per day (regimen B). And the last group received regimen B for the first week and regimen A for the second week (regimen C).

Furazolidone and metronidazole were packed in similar containers and provided to the patients along with other medications by the caring

physician. Each package was identified with a code and the codes were broken at the end of the study.

In addition to demographic data, we sought and recorded the smoking habits, NSAID consumption, history of PUD, and previous bleeding from PUD. We also recorded the size, number, and location of the ulcer(s) on endoscopy as well as presence of bulbar deformity and other endoscopic findings.

The patients were instructed about the use of the medications and probable side effects and were advised to contact their physician or a central managing physician (Y.A.) in case of any worrisome or problematic adverse effects. All patients were contacted one and two weeks after starting the treatment by the same physician (Y.A.). She checked the patient's compliance by counting the tablets remaining in the bottles and recorded any adverse events or newly started medications other than the study medications. Complete compliance was defined when the patients took at least 80% of the given drugs. Severity of each reported symptom was graded from 0 – 3 (0 not present, 1 mild, 2 moderate, and 3 severe or intolerable). Only moderate to severe adverse events were considered for analysis. Medications were discontinued if any intolerable adverse event occurred any appearance of fever, urticarial rash, or generalized body pain was noticed.

We invited all patients to take a ¹³C-urea breath test (UBT), ten weeks after completing the treatment. UBT was done with 75 mg of ¹³C-urea in fasting state solved in 100 mL of orange juice. The ¹³C in the expired air was measured 20 minutes later, using an infrared spectrophotometer (IRIS, Dr. Wagner, Bremen, Germany). The accuracy of cut-off values of UBT was evaluated in 22 patients without *H.pylori* infection (negative rapid urease test as well as absence of *H.pylori* in histologic examination of all five specimens, two taken from antrum, two from corpus, and one from fornix) and 30 patients with *H.pylori* infection (positive rapid urease test and/or positive histology). The sensitivity and specificity of the ¹³C-UBT were 90.0% and 95.6%, respectively. The cut-off value for negative UBT was less than 2.5 and for positive UBT was more than 4.5 (delta over base) (0/00).

We predicted that important side effects would be about 10% in group C, the same rate for group A, and 27% in group B. Having considered the 0.85 power to detect a significant difference

($P = 0.05$, two-sided), 92 patients were required for each study group. To compensate the patients who could not be evaluated fully, we planned to enroll 110 patients per group.

Chi-square was used for statistical analysis. The protocol was approved by the Ethics Committee of the Digestive Disease Research Center of Tehran University of Medical Sciences.

Results

Three hundred and fourteen patients were enrolled; 15 patients were lost to follow-up and 299 patients were followed at the second week. The baseline characteristics of the patients were comparable (Table 1). Twenty-one patients did not show up for the last follow-up for performing UBT; eight, seven, and six patients in groups A-C, respectively. Therefore, 278 patients completed the study and underwent ^{13}C -UBT at the tenth week. Sixteen patients had to discontinue their medication because of intolerable adverse drug reactions (three, seven, and six patients in groups A-C, respectively) and four patients were non-compliant (took less than 80% of the given medication, two, two, and zero patients in groups A-C, respectively). These 20 patients were not included in the per-protocol analysis. The flow chart shows these details (Figure 1).

Adverse events in the three groups are shown in Table 2. Fever, nausea, vomiting, dizziness, weakness, anorexia, and pruritus were significantly different between all groups ($P < 0.05$). The patients in the furazolidone-based group had significantly more side effects than those in the metronidazole-based group. The patients in the metronidazole group had no vomiting, no fever,

and did not complain of pruritus, which was seen in some patients treated with furazolidone-based regimen.

Frequency of most adverse events were higher when furazolidone was administered for two weeks compared with one week, but the difference was not significant except for fever, dizziness, and weakness ($P < 0.05$).

Rash, the most severe adverse reaction occurred in 12 patients. In nine patients it appeared in the second week and in three of the six patients in group C, the rash appeared after the end of the treatment with furazolidone.

Fever, another common side effect of furazolidone, appeared at the beginning of the second week except in one patient in group B. Sixteen patients had to discontinue the treatment because of intolerable adverse reactions. Of them, three were in the metronidazole-based, seven in the furazolidone-based, and six in the combination group ($P = \text{NS}$).

Intention to treat and per-protocol eradication rates are shown in Table 3. Eradication rates of 95.2% and 95.3% were achieved in the furazolidone-based and combination groups, respectively. These were significantly higher than that achieved in the metronidazole-based group (83.1%). Intention to treat eradication rates were also superior with regimens B and C (87.0% and 86.6%, respectively) than with regimen A (74.5%, $P < 0.05$).

Discussion

In recent years, furazolidone has been used successfully in the rescue therapy¹⁹⁻²³ as well as first-line treatment of *H. pylori* infection.²⁴⁻³³

Table 1. Characteristics of the patients and endoscopic findings.

| | Group A (n = 102) | Group B (n = 100) | Group C (n = 97) | |
|----------------------------------|-------------------------------------|----------------------|---------------------|------|
| Male/Female (n) | 68/34 | 62/38 | 59/38 | |
| Mean age \pm SD (years) | 42 \pm 14 | 44 \pm 14 | 43 \pm 14 | |
| Current smokers (%) | 18.6 | 16.0 | 15.5 | |
| History of GI bleeding (%) | 15.7 | 13.0 | 17.5 | |
| History of NSAID consumption (%) | 24.5 | 16.0 | 21.7 | |
| Endoscopic findings (n = 291) | DU (n) | 63 | 67 | 71 |
| | GU (n) | 4 | 3 | 3 |
| | Prepyloric ulcer (n) | 2 | 2 | 3 |
| | DU + GU (n) | 8 | 4 | 0 |
| | Scar only (n) | 2 | 0 | 1 |
| | Erosive duodenitis alone (n) | 17 | 24 | 18 |
| | Ulcer size \geq 8mm (%) (n = 201) | 54.7 | 63.9 | 56.0 |
| Bulb deformity (%) (n = 242) | 38.8 | 54.3 | 55.6 | |

A = 2 weeks metronidazole-based regimen; B = 2 weeks furazolidone-based regimen; C = 1 week furazolidone + 1 week metronidazole-based regimen.

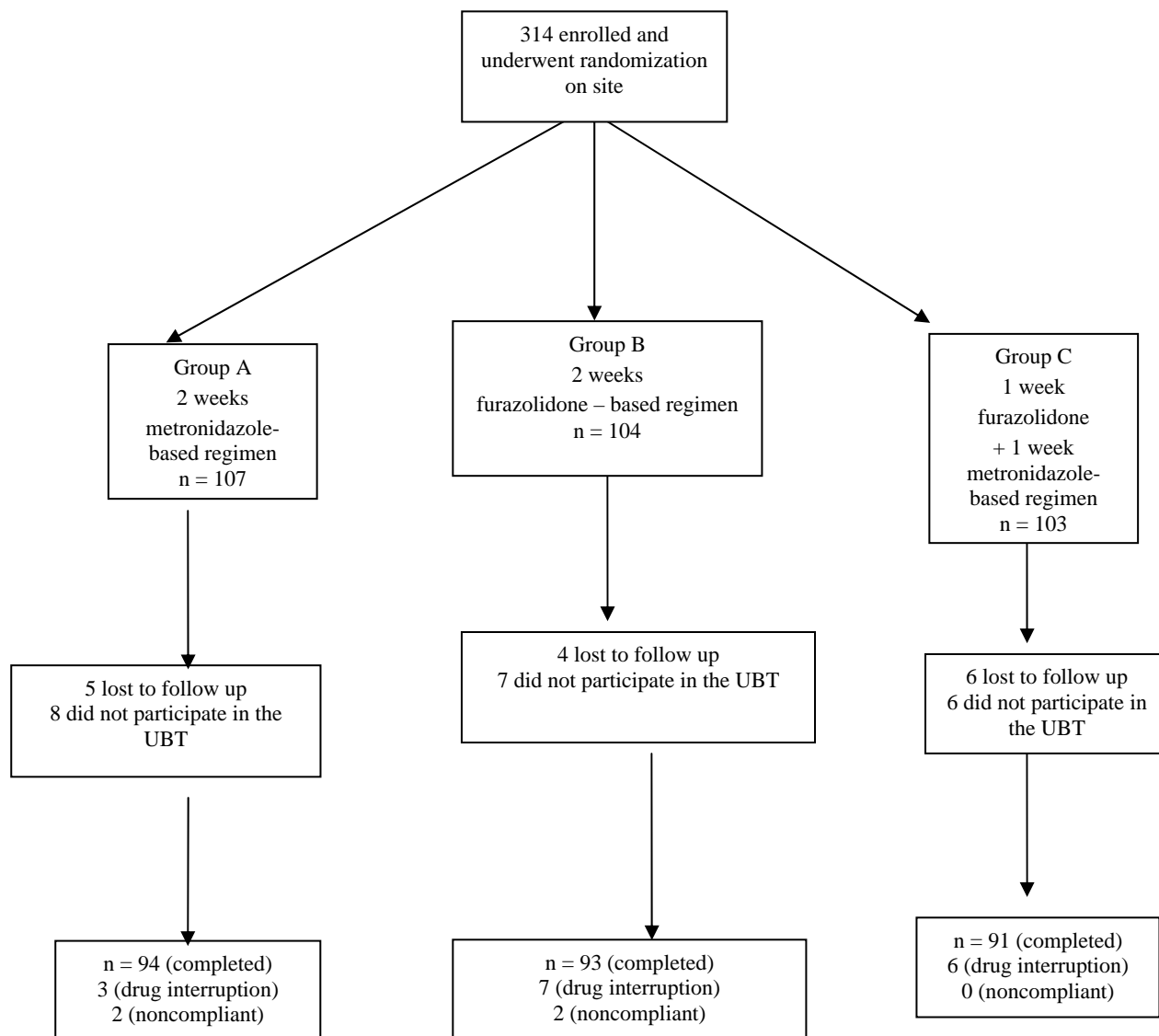


Figure 1. Flow chart of the patients.

Eradication rates of around 80% can be achieved when furazolidone is combined with one or two other antibiotics and an acid-suppressing drug.^{24, 25, 28 – 29, 32}

Despite this advantage, adverse reactions to furazolidone, which usually occur in the second week of treatment and lead to interruption of the treatment in many instances, limit its use.^{15, 17} Fever, rash, and generalized weakness associated with body pain are the most common reactions leading to premature discontinuation of furazolidone.

Furazolidone at doses less than 400 mg per day, which is associated with fewer adverse effects is not effective for eradication of *H.pylori*.^{17, 18} On the other hand, eradication rates of metronidazole-based regimens are at best 50 – 60% because of

high prevalence of drug-resistance.^{24, 27} Therefore, we tested the hypothesis of combining furazolidone and metronidazole in a two-week sequential therapy with the hope of keeping the high eradication rate of furazolidone while minimizing its adverse reactions.

Our data show that administering furazolidone for one week followed by metronidazole in a quadruple anti-*H.pylori* treatment regimen has an eradication rate similar to that of the two weeks furazolidone-based regimen, and will make it reasonably tolerable without sacrificing efficacy. Zullo et al have shown that the administration of amoxicillin for five days followed by clarithromycin and tinidazole for another five days is more effective than amoxicillin and clarithromycin given for seven days, both

Table 2. Reported adverse effects.

| | Group A (n = 102) | Group B (n = 100) | Group C (n = 97) |
|----------------------------------|----------------------|----------------------|---------------------|
| Fever * | 0 | 7 ** | 1 |
| Bad taste | 5 | 2 | 4 |
| Dry mouth | 3 | 2 | 1 |
| Nausea * | 3 | 13 | 7 |
| Vomiting * | 0 | 6*** | 4 *** |
| Abdominal pain | 2 | 4 | 6 |
| Dizziness * | 0 | 12 ** | 2 |
| Weakness * | 4 | 19 ** | 7 |
| Anorexia * | 1 | 9 | 5 |
| Bloating | 2 | 4 | 1 |
| Headache | 1 | 5 | 4 |
| Pruritus * | 0 | 3 | 6 *** |
| Skin rash | 1 | 5 | 6 *** |
| Discontinuation of treatment (n) | 3 | 7 | 6 |

A = 2 weeks metronidazole-based regimen; B = 2 weeks furazolidone-based regimen; C = 1 week furazolidone + 1 week metronidazole-based regimen; * $P < 0.05$ between all groups; ** $P < 0.05$ compared with C; *** $P < 0.005$ compared with A.

Table 3. Eradication rate of *H.pylori* in the three groups.

| | Group A | Group B | Group C |
|--------------------|------------|------------|------------|
| Per-protocol | 74/89 | 80/84 | 81/85 |
| Analysis (n = 258) | (83.1%) | (95.2%)* | (95.3%)* |
| (CI: 95%) | (74 – 90%) | (88 – 98%) | (88 – 98%) |
| Intention to treat | 76/102 | 87/100 | 84/97 |
| Analysis (n = 299) | (74.5%) | (87.0%)** | (86.6%)** |
| (CI: 95%) | (64 – 82%) | (78 – 92%) | (78 – 92%) |

A = 2 weeks metronidazole-based regimen; B = 2 weeks furazolidone-based regimen; C = 1 week furazolidone + 1 week metronidazole-based regimen; * $P < 0.005$ compared with A; ** $P < 0.02$ compared with A; CI = confidence interval.

combined with rabeprazole.³³

In this study, the duration of treatment in the nonsequential arm was three days shorter than the arm with the sequential therapy. This is probably the cause of the lower eradication rate.

In our study, the overall adverse effects were significantly lower in group C than in group B, while the number of patients who discontinued treatment because of adverse drug reactions were almost similar in groups B, C, and A (seven, six, and three, respectively, $P = NS$). Although two weeks metronidazole-based regimen had fewer side effects, the lower eradication rate of this regimen makes it unsuitable as the first-line anti-*H.pylori* regimen.

We have previously shown that a seven-day combination regimen does not achieve acceptable eradication rates.⁵⁻⁸ Considering this fact and the findings of the present study, which show that one week metronidazole followed by one week furazolidone has fewer side effects without sacrificing efficacy, it may be plausible to try an intermediate regimen to improve the side effect profiles of the combination regimen. This should be examined in further trials.

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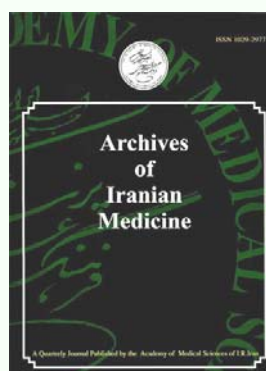
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