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RAPID COMMUNICATION

Azithromycin in one week quadruple therapy for *H pylori* eradication in Iran

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Abstract

AIM: To investigate eradication rates, patient compliance and tolerability of a 1-wk Azithromycin-based quadruple therapy versus the 2-wk conventional therapy.

METHODS: A total of 129 *H pylori*-positive patients were randomized to either omeprazole 20 mg, bismuth subcitrate 240 mg, azithromycin 250 mg, and metronidazole 500 mg, all twice daily for 1-wk (B-OAzM) or omeprazole 20 mg, bismuth subcitrate 240 mg, amoxicillin 1g, and metronidazole 500 mg all twice daily for 2-wk (B-OAM). *H pylori* infection was defined at entry by histology and rapid urease test and cure of infection was determined by negative urea breath test.

RESULTS: *H pylori* eradication rates produced by B-OAzM and B-OAM were 74.1% and 70.4% respectively based on an intention to treat analysis, and 78.1% versus 75.7% respectively based on a per-protocol analysis. The incidence of poor compliance was lower, although not significantly so, in patients randomized to B-OAzM than for B-OAM (3.5% versus 4.3%) but intolerability was similar in the two groups (35% versus 33.3%).

CONCLUSION: 1-wk azithromycin based quadruple regimen achieves an *H pylori* eradication rate comparable to that of standard 2-wk quadruple therapy, and is associated with comparable patient compliance and complications.

Key words: Peptic ulcer; Treatment; Azithromycin; *H pylori*; Non-ulcer dyspepsia

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INTRODUCTION

H pylori is a common human pathogen that has been shown to be a major factor in peptic ulcer disease. It has also been linked to gastric adenocarcinoma and gastric lymphoma[1].

A number of antimicrobial agents have been used in various regimens to eradicate *H pylori*. Clinical trails are regularly undertaken to search for simpler but equally effective regimens[2-4]. Azithromycin, a new generation macrolide, has some special attributes that suggest it would be a promising compound to be used in regimens for *H pylori* eradication. It is acid-stable, has a long half-life and achieves remarkably high concentration in the gastric tissue[3,5]. There have been several clinical trials of azithromycin for the therapy of *H pylori* infection[3,4,6,7]. As the pharmacological properties of azithromycin make it possible to use shorter courses, the problem has been to define an optimal dose and duration of azithromycin treatment in the course of therapy[3,4]. On the other hand, in developed countries, regimens of one week's duration are recommended for *H pylori* eradication[1,2] but in developing countries 1-wk regimens failed to eradicate the microbe. A minimum of 10 to 14 d of treatment were needed for eradication of the microbe, even in the presence of a favorable sensitivity profile[8-10]. The aim of this study was to assess the efficacy of azithromycin in a 1-wk regimen compared with a conventional 2-wk regimen in Iran, so we compared two quadruple regimens; bismuth subcitrate, omeprazole, azithromycin, and metronidazole, for 1-wk (B-OAzM) and bismuth subcitrate, omeprazole, amoxicillin and metronidazole, for 2-wk (B-OAM) in *H pylori* eradication. The safety and tolerability of the two drugs combinations were also evaluated and compared.

MATERIALS AND METHODS

Patients considered for the study included individuals 18-80 years old with upper GI symptoms that were referred to our gastroenterology clinic for upper endoscopy. Patients with *H pylori* infection were included in the study. Other inclusion criteria included indication for treatment as per the National Institutes of Health (NIH)

Table 1 Clinical and demographic data of patients in the treatment groups

Data	B-OAM-2 wk regimen *n* (%)	B-OAzM-1 wk regimen *n* (%)	*P* value[1]
ITT analysis	71	58	
Age: yr, Mean (SD)	48.3 (7.4)	46.7 (5.4)	0.17
Male	45 (63.3)	33 (56.8)	0.45
NSAID users	21 (29.5)	15 (25.8)	0.63
Cigarette smokers	11 (15.4)	8 (13.7)	0.78
Abdominal pain	47 (66.1)	31 (53.4)	0.14
Heartburn	14 (19.7)	18 (31)	0.13
Dyspepsia	57 (80.2)	40 (68.9)	0.13
PU	37 (52.1)	25 (43.1)	0.3
Non-ulcer dyspepsia	34 (47.8)	33 (56.8)	0.3
Loss to follow up	2	1	
Poor compliance	3	2	
Drop-outs	5	3	
PP analysis	66	55	

[1]*t*; for means and χ^2 for proportions, ITT; intention to treat, PP; per protocol.

Consensus Conference including: peptic ulcer disease, history of peptic ulcer, chronic gastritis, gastric mocusa associated lymphoid tissue, or intestinal metaplasia[1,7]. Between October 2003 and October 2004, a total of 129 patients were enrolled in the study. All patients gave written informed consent before entering the study and the protocol was reviewed and approved by the Semnan Gastrointestinal and Liver diseases Research Center. The criteria for exclusion were: intake of proton pump inhibitors, antibiotic or bismuth salts within 4 wk prior to the study, stomach surgery, known hypersensitivity to one of the study medications, patients with liver cirrhosis, renal failure or other serious severe concomitant illness, pregnant women, and patients who had previously undergone eradication therapy. These criteria were ascertained by taking a complete history, physical examination, and appropriate hematological and biochemical tests. The demographic and endoscopic data of these patients are reported in Table 1.

On initial endoscopy, *H pylori* infection was deter-mined by rapid urease test and histological assessment. Rapid urease test was performed using two biopsy specimens; one from the antrum and the other from the corpus[11]. Histological assessment of *H pylori* status was performed using one further biopsy specimen from the antrum; within 3 cm of the pylorus (hematoxylin-eosin and Giemsa stains)[12]. The patients were considered to be infected if both the urease test and histology were positive on initial testing. The patients that satisfied the inclusion criteria were randomly assigned to one of the following regimes; one group received a regimen of bismuth subcitrate 240 mg, omeprazole 20 mg, azithromycin (Azithromycin TC ®, Tehran shimi, Iran) 250 mg and metronidazole 500 mg, all bid, for 1-wk (B-OAzM) and the second group received a regimen of bismuth subcitrate 240 mg, omeprazole 20 mg, amoxicillin 1 g and metronidazole 500 mg, all bid, for 2-wk (B-OAM). Patients with duodenal or gastric ulcers continued on omeprazole (20 mg/d) for a total of 1 mo. Repeat examination was performed 1 wk and 4-8 wk after the cessation of therapy. Subjects recorded any side effects and change in symptoms, and performed an exit interview and pill count to evaluate compliance and side effects. Hematological and biochemical analyses were performed at the last visit. *H pylori* infection was determined by urea breath test (UBT) at the second examination. All patients were instructed to discontinue all proton pump inhibitors, H2 blockers, and bismuth for at least 4 wk before UBT. Eradication was defined on the basis of a negative UBT (carbon 13-Isomax 2000 TM device); results under the 5 cut off were considered negative[13].

Analysis of the two groups was conducted in the form of both per protocol (PP) and intention to treat (ITT). The ITT analysis for eradication was defined before the study to include all subjects who were randomized and received at least one dose of medication. The PP analysis for eradication included all subjects who took at least 80% of each study medication as prescribed.

The comparison of efficacy was evaluated using the χ^2 test. The analysis was performed using the SPSS 11.5 statistical package (SPSS, Chicago, IL).

RESULTS

The two groups were comparable in terms of common clinical variables that are summarized in Table 1. Three patients were lost to follow up (two from the B-OAM regimen and one subject from the B-OAzM regimen); also five patients discontinued the drugs because of severe side effects (three from the B-OAM regimen and two subject from the B-OAzM regimen). The remaining 121 patients completed the study as planned.

PP analysis: *H pylori* infection was eradicated in 43 of 55 patients in the B-OAzM group (78.18%, CI0.95: 64.98%-88.18%) and in 50 of 66 patients in the B-OAM group (75.75%, CI0.95: 63.63%-85.46%); the difference was not statistically significant ($\chi^2 = 0.1$, $P = 0.75$).

In patients with peptic ulcer, *H pylori* infection was eradicated in 19 of 25 patients in the B-OAzM group (76%, CI0.95: 54.87%-90.64%) and in 28 of 37 in the B-OAM group (75.67%, CI0.95: 58.8%-88.22%); the difference was not statistically significant ($\chi^2 < 0.001$, $P = 0.97$).

ITT analysis: *H pylori* infection was eradicated in 74.13% (CI0.95: 60.95%-84.74%) in the B-OAzM group and 70.42% (CI0.95: 58.4%-80.67%) in the B-OAM group; the difference was not statistically significant ($\chi^2 = 0.3$, $P = 0.58$).

Complications: the overall results for side effects are summarized in Table 2. Complications were noted in 14 patients in the B-OAzM group (25.45%) and 17 patients in the B-OAM group (25.75%) with no statistically significant differences between the groups ($\chi^2 < 0.001$, $P = 0.96$). The symptoms were mild and did not necessitate any additional treatment except in the five patients that discontinued the drugs for severe complications.

DISCUSSION

Although various regimens have been recommended for *H pylori* eradication, all of them include at least 2 antibiotics and one acid inhibitory drug[1]. In western countries,

Table 2 Complications of drugs in *H pylori* treatment

Complication	B-OAM-2 wk regimen	B-OAzM-1 wk regimen	*P* value[2]
n	69[3]	57[3]	
Diarrhea (%)	4 (5.7)	4 (7)	
Vomiting (%)	5 (7.2)[1]	4 (7)[1]	
Abdominal pain (%)	7 (10.1)	5 (8.7)	
Bad taste (%)	7 (10.1)	5 (8.7)	
Anal pain (%)	0	2 (3.5)	
Total (%)	23 (33.3%)	20 (35%)	0.83

[1]Three patients of group "A" and two patients of group "B" excluded from the study for severe vomiting.; [2] χ^2; [3] All patients except lost to follow up cases.

the most effective and usual regimens for preliminary treatment include; triple regimens for at least 1 wk, and use of clarithromycin as the antibiotic of choice against *H pylori*. Metronidazole, on the other hand, has largely been eliminated from first-line *H pylori* therapy because of its intolerability and high drug resistance[14]. However, in developing countries, effective treatments for *H pylori* vary from those used in developed countries. For example in middle east countries it has been shown that one week regimens fail to eradicate the microbe and the course of treatment should be continued for at least 10-14 d to provide for eradication[8-10]. Further, clarithromycin is not appropriate use because of its high price, drug resistance and unavailability[15,16], and so metronidazole is a common and effective drug in *H pylori* treatment in this setting.

Although the prevalence of *H pylori* strains that are resistant to metronidazole varies from 46%-51% in Iran[15-17], it has been shown that this drug in high doses (> 1 g) and in combination with other drugs remains effective against *H pylori*[18-21]. Therefore, in Iran as also done in some Asian countries[14,18] metronidazole is a very common drug used in *H pylori* eradication regimens[22]. In Iran, the most common regimens for first-line treatment are 2-wk quadruple regimens that include; metronidazole, omeprazole, bismuth and tetracycline or amoxicillin[22]. This conventional regimen introduced initially by Hosking, Deboer, Borody, and Laine as an effective regimen in *H pylori* treatment has confirmed efficiency of a 63%-93% eradication rate[7,23-25]. On other hand, due to high rates of resistance to metronidazole, furazolidine was used instead of it, as first or particularly second line treatment[26].

Although 2 wk regimens have been effective in *H pylori* eradication, some patients withdraw from their treatment because of the long duration and large number of tablets. Thus, in this study we showed that a quadruple regimen, where azithromycin replaced amoxicillin, the duration of the treatment can be decreased without any change in its effectiveness.

Azithromycin is a new macrolide related to clarithromycin with an effective role in *H pylori* eradication and it was reported that azithromycin has a synergic effect with esomeprazole, even in presence of drug resistance[27]. In various studies the effectiveness of azithromycin has been evaluated in different doses from 500 mg to 3 g[2,27-29], although in most studies this drug was used for 3 d (1.5 g) as in respiratory tract infection but at this dose it has less effect than clarithromycin[3,5]. However, by increasing the total dose to 3 g, it has been shown that the effectiveness of azithromycin can be restored[3,4,6,7].

This is the first study in which azithromycin was used at a prescribed amount of 3.5 g (250 mg bid for 7d) in the treatment of *H pylori* infection. Fortunately; the patients' tolerance was excellent. There were a few side effects based on biochemical tests, but most side effects were mild and disappeared with conservative therapy without the need to terminate the treatment.

Finally, in areas where clarithromycin cannot be used because of drug resistance or unavailability, azithromycin with a total dose of 3.5 g is an appropriate and safe drug for *H pylori* eradication regimen.

The effectiveness of furazolidone based *triple or quadruple regimens* has been evaluated in Iran[15,22,25,26], but because of resistance to metronidazole, it seems possible that a combination of azithromycin and furazolidone instead of azithromycin and metronidazole will achieve more favorable eradication rates, although further evaluation is needed.

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