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Original Article

Helicobacter Pylori Ran Away Furazolidone-based Quadruple Therapy!

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Abstract

Background: *Helicobacter pylori* is the main etiologic agent in most gastritis and peptic ulcers **.** The ideal regimen for the treatment of *H. pylori* infection has not yet been defined**.** This study was designed to evaluate the eradication rate of *H. pylori* infection using a short-term and cost effective furazolidone-based regimen in a previously sensitive area to furazolidone drug.

Methods: In a randomized single blinded clinical trial study, 135 patients with an endoscopically verified *H. pylori*-positive peptic ulcer disease were randomly assigned to a quadruple therapy of "furazolidone, 200 mg; bismuth subcitrate, 240 mg; tetracycline, 500 mg and omeprzole, 20 mg" twice daily for either 14 or 7 days. Six-eight weeks after cessation of therapy, *H. pylori* eradication was assessed by ^{13}C-urea breath test.

Results: *H. pylori* eradication rate in 7-day and 14-day groups were 71% and 65%, respectively using intention to treat test with no significant difference between the two groups. *H. pylori* eradication rate had no significant correlation with age, sex and smoking habit.

Conclusion: Our study showed that furazolidone-based regimen could not yield an acceptable eradication rate in the area sensitive to furazolidone previously. Eradication failure was attributed to several reasons including inadequate choice of drugs, insufficient knowledge of best therapeutic choices; poor patients' adherence to treatment and primary *H. pylori* resistance to the most commonly employed antibiotics.

Keywords: Eradication; *H. pylori*; Resistance; Furazolidone

Introduction

Helicobacter pylori is the main etiologic agent of most gastritis and peptic ulcers,[1-4] which is present in 95-99% of duodenal ulcers and most gastric ulcers, too.[5-9] Eradication of infection leads to resolution of the gastritis and to spectacular decrease of duodenal and gastric ulcer relapses.[10-13]

The ideal regimen (>90% eradication rate) for the treatment of *H. pylori* infection has not yet been defined.[14-16] The antibiotics used in *H. pylori* regimens differ in their susceptibility to the acid secretion. Metronidazole is very stable in gastric juice at pH=2 and 7.[17,18] However, its resistance is a rising problem worldwide, particularly in developing countries like Iran which limits the usefulness of this drug.[19,20]

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Furazolidone, an old inexpensive antibiotic was shown to be a good alternative to metronidazole in triple therapy for *H. pylori* eradication in the areas where metronidazole resistance is common.[21-25]

Previous studies have shown that a 14-day furazolidone-based triple therapy is the most suitable for *H. pylori* eradication in Iran, with an eradication rate close to 90% and a lower cost than other effective regimens. Unfortunately with this regimen, some patients exhibited severe adverse effects or could not tolerate furazolidone. Thus, a study on the efficacy of lower dose of furazolidone or shorter courses would be of interest.[26-29]

This study was designed to evaluate the eradication rate of *H. pylori* infection using a short-term and low-cost furazolidone-based regimen in a previously sensitive area to furazolidone in Guilan Province, northern Iran.

Materials and Methods

In a randomized single-blinded clinical trial study, conducted from July 2004 to July 2005, a total of 135 patients with an endoscopically verified *H. pylori*-positive peptic ulcer disease were recruited and randomly received the therapeutic regimen (the cases were selected according to the even or odd numbers assigned to them) of "furazolidone, 200 mg; bismuth subcitrate, 240 mg; tetracycline, 500 mg and omeprzole, 20 mg" twice daily for either 14 or 7 days. All patients were informed verbally and signed informed consents before recruitment. Patients were excluded if they had a co-morbid condition, recent intake of steroids, NSAIDs, proton pomp inhibitors or antibiotics in the previous 4 weeks or had a known history of drug allergy. At the end of therapy, all patients were visited for the assessment of compliance and side effects. Six to eight weeks after cessation of therapy, *H. pylori* eradication was assessed by,[13] C-urea breath test (UBT). *H. pylori* eradication was considered if the test was negative. The demographic data and endoscopic findings, side effects and eradication rate of both groups were compared using the logistic regression test. Analysis was performed using SPSS software (version 10, Chicago, IL, USA) and the level of significance was 0.05.

Results

Out of 135 patients, 74 were in 14-day and 61 in 7-day groups but 130 patients completed the study. Fifty-four (40%) were male, 24 (%18) were smoker and 12 (50%) and 12 (50%) were in 7-day and 14-day groups, respectively. Five patients (3.7%) discontinued the therapy due to some adverse effects such as high fever and rash that all were noticed in 14-day group but others showed no significant side-effect. *H. pylori* eradication rate in 7-day and 14-day groups were 71% and 65% respectively which had no significant difference after adjustment for age, sex and smoking. *H. pylori* eradication rate had no significant correlation with age, sex and smoking habit (Table 1).

Discussion

In Iran, many studies have addressed the issue of the optimal treatment for *H. pylori* eradication.[30,31] Two weeks quadruple therapy with proton pomp inhibitors or H_2-blockers, bismuth, metronidazole and amoxycillin or tetracycline is known to be one of the most effective regimens for *H. pylori* eradication, but according to studies in Iran, the quadruple regimens always result in a suboptimal eradication rate.[21,32] This is most likely due to the high metronidazole resistance rate of *H. pylori* reported from Iran.[14,31] Furazolidone is an antibiotic that due to its theraputic spectrum and low cost is a good alternative for metronidazole in triple therapy for *H. pylori* eradication in areas where metronidazole resistance is common.[29,33]

Table 1: The correlation between smoking and *H. pylori* eradication (negative UBT) by duration of therapy (*P*>0.05).

Duration of therapy for smoker		Positive UBT No. (%)	Negative UBT No. (%)	*P Value*
7-days	Smoker	6(50)	6(50)	0.068
	Non-smoker	12(25)	37(75)	
14-days	smoker	6(50)	6(50)	0.07
	Non-smoker	18(32)	39(68)	

In one study in Iran, eradication rate of *H. pylori* using ranitidine, amoxicillin, bismuth subcitrate with either furazolidone or metronidazole for two weeks were 82% and 56%, respectively.[21] In another study, eradication of *H. pylori* in duodenal ulcer disease using tetracycline and fourazolidone vs. metronidazole and amoxicillin in an omeprazole-based triple therapy (TFO vs. MAO) for two weeks were 96.3% and 83.3%, respectively.[27] But a major problem with furazolidone at the standard dose of 200 mg, twice daily for two weeks is the high rate of severe adverse effects. Most of these adverse effects are related to its role as a monoamino-oxidase inhibitor and include fever, rash and severe abdominal pain. Such adverse effects may lead to the discontinuation of treatment in some patients; thus, a study on the efficacy of lower doses of furazolidone or shorter courses would be of interest.[28]

So we designed a shorter course of study on the population of same area where *H. pylori* eradication using TFO for two weeks was 96.3% three years ago, but bismuth subcitrate was added and duration of therapy decreased to 7 days. The study showed that furazolidone-based regimen could not yield an acceptable eradication rate in the area which was sensitive to furazolidone previously (71% vs. 96.3%).[27] There was no significant difference in *H. pylori* eradication rate between 7 and 14 day treatments. Five patients discontinued therapy who all were in 14-day group. Perhaps it can justify the lower eradication rate of 14-day in comparison with 7-day group.

This study also revealed that resistance to furazolidone has increased. Eradication failure might have been due to several reasons including inadequate choice of drugs, lack of knowledge of best therapeutic options, poor patients' adherence to treatment and primary *H. pylori* resistance to the most commonly employed antibiotics, which is a major concern.[34,35] The notion of the development of super *H. pylori* resistant to most antibiotics should increase the awareness of physicians and scientists on the need for a rational approach to this particular infection.[36]

The newer generation of fluoroquinolones showed some promise as part of an eradication regimen. Gatfloxacin is well absorbed from the gastrointestinal tract and *in vitro* susceptibility studies have not suggested any resistance problems so far. In a study, the efficacy of gatfloxacin in combination with amoxycillin and rabeprazole for 7 days in 104 patients was evaluated. The infection was cured in 48 of 52 patients (92%).[37]

Recent biopsy studies[38,39] and cell culture infection models[40,41] have provided increasing evidence for the intracellular localization of *H. pylori*. Therefore, access of antimicrobial drugs to the site is restricted from both the lumen of the stomach and the gastric blood supply. As conventional drug delivery systems do not remain in the stomach for prolonged periods, they are unable to deliver the antibiotics to the site of infection in effective concentrations and in fully active forms. Therefore, it is necessary to design drug delivery systems that can not only alleviate the short comings of conventional delivery vehicles but also deliver the antimicrobials to the infected cell lines. The use of nanoparticles could be of interest for bioadhesion purposes, because these pharmaceutical dosage forms have a large specific surface indicative of a high interactive potential with biological surfaces. Gliadin appears to be a suitable polymer for the preparation of mucoadhesive nanoparticles capable of adhering to the mucus layers. The preferential accumulation of nanoparticles in the stomach may be very helpful in targeting the antibiotics at the site of infection and possibly also for *H. pylori* eradication. In a study, amoxicillin gliadin nanoparticles (AGNP) could eradicate *H. pylori* from the gastrointestinal tract more effectively than amoxicillin because of the prolonged gastrointestinal residence time attributed to mucoadhesion.[42] A dosage form containing mucoadhesive nanoparticles bearing a potential antibiotic should be useful for the complete eradication of *H. pylori*.[43]

Alternative modes of treatment, particularly non-toxic, natural, and inexpensive products like plant extracts, probiotic agents and cobalt are warranted. Unfortunately, these experimental therapies rarely, if ever, can cure the infection while in some cases may temporarily suppress the bacteria.

So regimens for eradication of *H. pylori* need to be re-evaluated in view of emerging resistance to antibiotics. In doing so, therapy for treatment failure may be improved by assessing antimicrobial sensitivity.[38]

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Conflict of interest: None declared.

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