BRIEF ARTICLE

Quadruple therapy with moxifloxacin and bismuth for first-line treatment of *Helicobacter pylori*

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Received: June 6, 2012   Revised: July 20, 2012
Accepted: July 28, 2012
Published online: August 28, 2012

Abstract

AIM: To compare triple therapy *vs* quadruple therapy for 10 d as first-line treatment of *Helicobacter pylori* (*H. pylori*) infection.

METHODS: Consecutive *H. pylori* positive patients never treated in the past for this infection were randomly treated with triple therapy of pantoprazole (PAN) 20 mg bid, amoxicillin (AMO) 1 g bid and moxifloxacin (MOX) 400 mg bid for 10 d (PAM) or with quadruple therapy of PAN 20 mg bid, AMO 1 g bid, MOX 400 mg bid and bismuth subcitrate 240 mg bid for 10 d (PAMB). All patients were found positive at 13 C-Urea breath test (UBT) performed within ten days prior to the start of the study. A successful outcome was confirmed with an UBT performed 8 wk after the end of treatment. χ^2 analysis was used for statistical comparison. Per protocol (PP) and intention-to-treat (ITT) values were also calculated.

RESULTS: Fifty-seven patients were enrolled in the PAM group and 50 in the PAMB group. One patient in each group did not return for further assessment. Eradication was higher in the PAMB group (negative: 46 and positive: 3) *vs* the PAM group (negative: 44 and positive: 12). The *H. pylori* eradication rate was statistically significantly higher in the PAMB group *vs* the PAM group, both with the PP and ITT analyses (PP: PAMB 93.8%, PAM 78.5%, *P* < 0.02; ITT: PAMB 92%, PAM 77.1 %, *P* <0.03).

CONCLUSION: The addition of bismuth subcitrate can be considered a valuable adjuvant to triple therapy in those areas where *H. pylori* shows a high resistance to fluoroquinolones.

INTRODUCTION

Helicobacter pylori (*H. pylori*) has an important role in the

development of chronic gastritis and peptic ulcer disease and has been linked to the pathogenesis of gastric lymphoma and gastric cancer[1-3], hence it is recommended that this infection be cured whenever it is diagnosed. *H. pylori* is susceptible to several antibiotics including clarithromycin, amoxicillin (AMO), metronidazole, tinidazole, tetracycline, rifabutin and fluoroquinolones [levofloxacin and moxifloxacin (MOX)][4,5], and is inherently resistant to many other antibiotics such as bacitracin, vancomycin, trimethoprim, polymyxins and nalidixic acid[6,7]. This bacterial infection, however, has proven challenging to cure. There are several reasons for the loss of eradication efficacy, and antibiotic resistance is the key factor for treatment failure[8]. Resistance rates vary in different geographic areas and therefore the selection of therapeutic regimes needs adjustments according to local resistance pattern[9,10]. The prevalence of antibiotic resistance in various regions is correlated with general use of antibiotics in the region[11,12].

Classical triple therapies with proton pump inhibitors (PPI) clarithromycin and AMO or metronidazole are the mainstay of current treatment, but resistance to clarithromycin has been reducing its effectiveness in recent years, with an eradication rate below 80% of treated cases[13,14]. In geographic areas with high clarithromycin resistance, bismuth-containing quadruple therapy is superior to standard triple therapy. The original quadruple therapy based on omeprazole, bismuth subcitrate, metronidazole and tetracycline achieves higher eradication rates compared with the standard triple therapy[15,16]. In a recent randomized, open-label, phase 3 trial, a quadruple regimen with a capsule containing bismuth citrate potassium, metronidazole, and tetracycline given with omeprazole was found more efficacious than a clarithromycin-based triple therapy in patients never treated in the past for the infection[17].

MOX-based triple therapy has been suggested as an alternative first-line therapy for *H. pylori* infection in geographical areas with clarithromycin resistance exceeding 30% of strains. Eradication rates of up to 92% in the MOX-based triple regimens compared to 79% in the clarithromycin-based regimens were demonstrated[18]. Primary resistance of *H. pylori* strains collected from patients who have never been treated in the past for *H. pylori* infection to fluoroquinolones has been reported to be lower than that of clarithromycin in several geographic areas[19]. Resistance to fluoroquinolones, however, rapidly develops in areas where these antibiotics are widely used. In our region in fact, the resistance rate of *H. pylori* to MOX has increased in the last two years from 12% in 2009 to 25% in 2011, while resistance to clarithromycin is stable, ranging from 40% to 59% (unpublished results). Similar results have been registered in other areas of the world. A recent study from Korea reports a steady increase of MOX resistance from 5.6% in 2004 up to 28.2% in 2008 with the need to optimize dosage and duration of treatment[20]. Treatment with MOX-based triple therapy for 10 d should be preferred over a 7-d course, and there is

evidence that a dose of 800 mg/d is superior to the 400 mg standard dose[21,22].

The aim of the study was to compare MOX containing triple therapy *vs* MOX and bismuth-containing quadruple therapy for first-line treatment of *H. pylori* infection.

MATERIALS AND METHODS

Eligibility criteria
Patients were enrolled among those with a positive ^{13}C urea breath test (UBT) performed with citric acid and 75 mg of ^{13}C urea performed within ten days prior to the start of the study. Exclusion criteria included: age <18 years or > 80 years; any previous treatment for *H. pylori* infection, treatment with PPI (omeprazole, lansoprazole, pantoprazole (PAN), rabeprazole, esomeprazole), H_2-blockers (ranitidine, nizatidine, cimetidine, famotidine, roxatidine), and/or antibiotics during the 4 wk before the study; gastrointestinal malignancy, severe concomitant diseases, previous gastric surgery. Further exclusion criteria were a prolongation of the QT interval, defined as the interval between the beginning of the QRS complex and the end of the T wave. QT interval was computed using an electrocardiogram (ECG) performed in all patients within 10 d prior to the beginning of the study.

Study protocol
Consecutive *H. pylori* positive patients never treated in their past for the infection were randomly treated with a triple therapy with PAN, AMO, MOX (PAM) or with a quadruple therapy with PAN, AMO, MOX and bismuth subcitrate (PAMB) for 10 d.

While PAN, AMO and MOX were administered before breakfast and supper, bismuth salts were administered 3 h after the administration of PAN, AMO, MOX, since it may bind in some patients with MOX and prevent its full absorption[23].

Dosages and time of administration of the studied drugs are summarized in Table 1. Patients were informed that bismuth renders the stools a black dark colour. Successful outcome was confirmed with an UBT performed 8 wk after the end of treatment with a Delta Over Baseline value equal or less than 5.

Determination of sample size
Sample size was predetermined taking the following parameters into consideration: α = 0.05; β = 0.20; lost to follow-up = 5%; expected eradication rate in the PAM group = 72%; expected eradication rate in the PAMB group = 95% (23% increase). With these parameters, the required sample size was equal to 90 patients per group.

Statistical analysis
Statistical evaluation was carried out using the χ^2 analysis. A *P*-value of 0.05 or less was considered statistically significant. Per protocol (PP), in which only data from adherent subjects are analyzed, and intention-to-treat (ITT), in

Table 1 Summary of study data	
Triple therapy regimen (PAM)	**Quadruple therapy regimen (PAMB)**
Pantoprazole 20 mg *bid* (8.00 am-8.00 pm)	Pantoprazole 20 mg *bid* (8.00 am-8.00 pm)
Amoxicillin 1 g *bid* (8.00 am-8.00 pm)	Amoxicillin 1 g *bid* (8.00 am-8.00 pm)
Moxifloxacin 400 mg *bid* (8.00 am-8.00 pm)	Moxifloxacin 400 mg *bid* (8.00 am-8.00 pm)
	Bismuth subcitrate 240 mg *bid* (11.00 am-11.00 pm)
Number of patients: 57	Number of patients: 50
Female/male: 30/27	Female/male: 28/22
Age: mean 49 yr, range 23-75 yr	Age: mean 50 yr, range 20-72 yr
Follow-up loss: 1	Follow-up loss: 1
UBT negative: 44	UBT negative: 46
UBT positive: 12	UBT positive: 3
Per protocol: 44/56 (78.5%)	Per protocol: 46/49 (93.8%)[a]
Intention to treat: 44/57 (77.1%)	Intention to treat: 46/50 (92%)[a]

[a]$P < 0.05$ *vs* pantoprazole, amoxicillin and moxifloxacin (PAM). PAMB: Pantoprazole, amoxicillin, moxifloxacin and bismuth subcitrate; UBT: Urea breath test.

which all subjects are followed regardless of adherence, evaluations were calculated.

RESULTS

Patient characteristics are summarized in Table 1. Fifty-seven patients were enrolled in the PAM group and 50 in the PAMB group. One patient in each group did not return for further assessment (Table 1). Results of UBT performed 8 wk after the end of treatment are shown in Table 1.

The eradication rate was the following for PP and ITT analysis: PAM group PP: 44/56 (78.5%), PAMB group PP: 46/49 (93.8%); PAM group ITT: 44/57 (77.1%), PAMB group ITT: 46/50 (92%). *H. pylori* eradication rate was statistically significantly higher in the PAMB group *vs* the PAM group, both with the PP ($P < 0.02$) or ITT analysis ($P < 0.03$) (Table 1).

Adverse effects

Both treatments were well tolerated with no reported side effects.

DISCUSSION

Triple therapy based on a PPI combined with clarithromycin and AMO and/or metronidazole has been the established first-line therapy for *H. pylori* infection over the past years around the world[24,25]. However, the efficacy of standard triple therapy needs to be reconsidered in areas with a high prevalence of clarithromicyn or metronidazole resistant *H. pylori* strains. The geographical prevalence of antibiotic resistance should influence the choice of a first-line regimen for the treatment of infection by *H. pylori*. Alternatively, new regimens with high eradication rates should be identified. Quadruple therapies have been used as second-line therapy, and have also been proven effective as first-line treatment in areas with a high prevalence of clarithromicyn-resistant *H. pylori* strains. Quadruple therapy containing bismuth has been used in the first-line therapy of *H. pylori* infection with variable results. Ching *et al*[26], from North Wales, United King-

dom, randomized patients to bismuth quadruple therapy or clarithromycin triple therapy. A total of 91% of patients receiving bismuth quadruple therapy and 92% of patients receiving clarithromycin triple therapy achieved successful *H. pylori* eradication. Calvet *et al*[27] performed a study in which patients were randomized to receive bismuth quadruple therapy or receive clarithromycin triple therapy. Eradication was achieved in 83% of the bismuth quadruple therapy group and 77% of the clarithromycin triple therapy group. In conclusion, in these two studies, first-line quadruple and triple therapies yielded similar eradication rates in the treatment of *H. pylori* infection.

Other studies have shown that the addition of bismuth to a first-line triple therapy produces high eradication rates despite the presence of high antibiotic-resistant strains. Malfertheiner *et al*[17] have recently shown that a quadruple therapy with omeprazole and a single three-in-one capsule containing bismuth citrate potassium, metronidazole and tetracycline for 10 d when compared with a triple therapy for 7 d with omeprazole, AMO, and clarithromycin produces an eradication rate of 80% *vs* 55% in the standard therapy group. The authors concluded that quadruple therapy needs to be considered as first-line therapy in areas with a high prevalence of clarithromycin-resistant *H. pylori* strains. These data are supported by results from a study from China in which bismuth was added to standard triple-therapy including PPI, clarithromycyn and AMO and the *H. pylori* eradication rate was above 90%. This treatment showed a higher efficiency than standard triple-therapy, and the addition of bismuth and prolongation of the treatment from 7 to 14 d helped to overcome clarithromycin resistance in 84% of the patients[28].

Our study shows that the addition of bismuth subcitrate to a triple therapy that includes PAN, AMO and MOX for first-line treatment of *H. pylori* infection significantly increases the eradication rate of the same therapy without bismuth. With bismuth included, eradication was 93.8% in PP and 92% in ITT analysis, but without bismuth the eradication rate was 78.5% in PP and 71.8% in ITT analysis. Indeed the same triple therapy used three years before the present study, induced a higher eradica-

tion rate[22]; this change is probably due to an increase in resistance to MOX in our region from 2009-2011 (increase from 12% to 25%). Unfortunately, the absence of a preliminary susceptibility test in our patients does not allow us to understand whether the low rate of eradication in PAM group is effectively due to increased resistance to MOX or if patients infected by *H. pylori* resistant to MOX were equally distributed in the two therapeutic groups. Therefore, a periodic surveillance of antibiotic resistance is necessary since some antibiotics may develop resistance much more easily than others, such as in the case of MOX[20]. The resistance against fluoroquinolones is mainly generated by mutations in the *gyrA* gene that encodes DNA gyrase[29,30]. The consequence of such a mutation is the inability of fluoroquinolones to inhibit DNA replication[31,32].

In our study the addition of bismuth to triple therapy has provided a therapeutic gain of 15% to a standard therapy. Bismuth exerts its antibacterial action by decreasing mucin viscosity, by binding toxins produced by *H. pylori*, and by preventing bacterial colonization and adherence to gastric epithelium[33,34]. In addition bismuth reduces the bacterial load and has a synergistic effect with antibiotics[35], particularly with the nitroimidazole family[36].

The use of bismuth has raised some concerns about its side effects. A meta-analysis of 35 randomized controlled trials was published to assess the safety of bismuth. It showed that no serious adverse events occurred with bismuth therapy, and bismuth for the treatment of *H. pylori* was safe and well-tolerated[37]. In our study, there have been no side effects reported.

Criticism for our study might include the absence of a preliminary susceptibility test in our patients. In fact, treatment failure in 12 patients in the PAM group was probably due to MOX resistance. However, the addition of bismuth to triple therapy helps to overcome *H. pylori* resistance to MOX: only 3 patients had a positive ^{13}C UBT after treatment with quadruple therapy. The addition of bismuth to standard therapy results in an improved eradication rate, therefore, bismuth may be considered as a valuable adjuvant to triple therapy in those areas *H. pylori* shows a high resistance to fluoroquinolones.

The 10-d quadruple therapy consisting of a PPI, bismuth, AMO, and MOX achieved ITT success of 93.8% and can be recommended as the first-line treatment of *H. pylori* infection in regions of high fluoroquinolones resistance.

ACKNOWLEDGMENTS

COMMENTS

Background
The standard treatment of *Helicobacter pylori* (*H. pylori*) infection is carried out by using a drug that inhibits gastric acid secretion associated with two antibiot-

ics represented by amoxicillin and clarithromycin or metronidazole. The success rate of this triple therapy varies from region to region worldwide, mainly due to a variation in antibiotic resistance. There is, therefore, a continuous search for new antibiotics that show low resistance against *H. pylori* or other substances that, when added to triple therapy, may overcome the obstacle of resistance.

Research frontiers
Fluoroquinolones are a relatively new class of antibiotics that may be highly efficacious against *H.pylori* infection. However, bacterial resistance to fluoroquinolones may rapidly increase over time due to their widespread use, especially for pulmonary and urinary tract infections. Recent studies have shown that the addition of bismuth subcitrate to a standard triple therapy may at least in part overcome the antibiotic resistance and improve the success rate of a standard triple therapy. In this study, the authors showed the adjunction of bismuth subcitrate to a triple therapy that includes the fluoroquinolone derivative, moxifloxacin, improved the success rate of the same therapy given without bismuth in a group of patients with *H. pylori* infection never treated in the past. The *H. pylori* infection had been diagnosed by means of urea breath test (UBT). To verify the effectiveness of the therapy, UBT was repeated in all patients 2 mo after the end of therapy.

Innovations and breakthroughs
To the knowledge, this is the first study that shows that bismuth improves the therapeutic effect of moxifloxacin for the treatment of *H. pylori* infection in patients never treated in the past for this infection.

Applications
The study offers an alternative therapeutic option for all who are involved in the treatment of *H. pylori* infection.

Terminology
UBT is the most accurate non-invasive test for the diagnosis of *H. pylori* infection and does not necessitate endoscopic intervention. The main limit of the test is that it results in false negative results if performed while the patient is taking drugs that may inhibit gastric secretion or antibiotics.

Peer review
The study is an important contribution to the growing body of literature on alternative therapies to treat the increasingly drug-resistant *H. pylori* isolates.

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