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Alimentary Tract

Levofloxacin, bismuth, amoxicillin and esomeprazole as second-line *Helicobacter pylori* therapy after failure of non-bismuth quadruple therapy

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ABSTRACT

Background: The best rescue therapy for *Helicobacter pylori* (*H. pylori*) infection following failure of non-bismuth quadruple therapy (NBQT) remains unanswered.
Aims: To determine the efficacy, safety and compliance of levofloxacin, bismuth, amoxicillin and esomeprazole (LBAE) regimen following failure of NBQT.
Methods: 132 patients with *H. pylori* infection refractory to first-line NBQT received LBAE regimen (levofloxacin 500 mg once/day, bismuth potassium citrate 220 mg twice/day, amoxicillin 1000 mg twice/day and esomeprazole 20 mg twice/day for 14 days). Gastric mucosal biopsy was obtained for *H. pylori* culture, antimicrobial sensitivity test and cytochrome P450 isoenzyme 2C19 polymorphism analysis.
Results: LBAE therapy achieved eradication rates of 73.5% [95% confidence intervals (CI) 65.9–81.1%] in intention-to-treat and 78.5% (71.1–85.9%) in per-protocol analyses in patients with high antibiotic resistance (amoxicillin 8.3%, clarithromycin 55.6%, metronidazole 73.6% and levofloxacin 36.1%). Adverse effects were found in 19.2% and compliance in 96.1% of the treated patients. Multivariate analyses identified levofloxacin resistance [odds ratio (OR) 7.183, 95% CI 1.616–31.914, $P = 0.010$] and history of quinolone intake (4.844, 1.174–19.983, $P = 0.029$) as independent predictors of treatment failure. The eradication rate of patients with dual amoxicillin and levofloxacin resistance was significantly decreased (33.3%, $P = 0.006$).
Conclusions: In populations with high levofloxacin resistance, 14-day second-line LBAE regimen resulted in an unsatisfactory efficacy in patients resistant to NBQT despite good safety and compliance.

1. Introduction

With the continuous increase in resistance to antibiotics, the efficacy of standard triple therapy for *Helicobacter pylori* (*H. pylori*) infection is unsatisfactory in many regions worldwide [1]. Non-bismuth quadruple therapy (NBQT), including sequential, concomitant and hybrid therapies, is widely used in clinical practice due to good eradication efficacy, safety profile and compliance [1,2]. Maastricht IV consensus also recommended NBQT as the empiric first-line regimen for the eradication of *H. pylori* in regions with high resistance to clarithromycin [2]. However, the best rescue therapy following failure of NBQT remains unanswered, as these patients have limited options for further therapy because they have already received three different relevant antibiotics: amoxicillin, clarithromycin and metronidazole.

Bismuth quadruple therapy, comprising proton pumper inhibitor (PPI), bismuth, tetracycline and metronidazole, has been recommended as the second-line rescue approach [2,3]. However, it is greatly restricted due to the difficulty in obtaining tetracycline in many regions, complex administration and high incidence of adverse reactions. Furthermore, the traditional quadruple regimen fails to eradicate *H. pylori* in approximately 20–30% of cases [3,4].

Levofloxacin-containing triple regimen, comprising PPI, amoxicillin and levofloxacin for 10 days, has also been recommended in Maastricht IV consensus as a second-line therapy [2]. However, recent studies suggested that the efficacy of levofloxacin-containing therapy is decreasing, most likely due to increased quinolone resistance [5–8]. A recent meta-analysis showed that

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the eradication rate of 10-day levofloxacin-amoxicillin-PPI therapy after failure of concomitant and sequential therapies was only 78% and 81%, respectively [9].

Bismuth is one of the few antimicrobials to which resistance is not developed [10,11]. In addition, bismuth has a synergistic effect with antibiotics and partially overcomes levofloxacin and clarithromycin resistance [10,12]. Thus, combining bismuth and levofloxacin in the same regimen may be a good option as rescue regimen.

Up to now, a total of six papers on the efficacies of *H. pylori* eradication with the quadruple regimen of levofloxacin, bismuth, amoxicillin and PPI have been published [4,12–16]. Although there have been some related study reports, as the second-line rescue therapy after failure of initial NBQT, only one paper has been published. Gisbert et al. reported the use of quadruple therapy comprising levofloxacin, bismuth, amoxicillin and esomeprazole (LBAE) for the patients refractory to first-line NBQT regimen with good efficacy [90.0% in intention-to-treat (ITT) analysis and 91.1% in per-protocol (PP) analysis], safety and compliance [4]. However, there are some limitations in the study, such as relatively small sample size, lack of *H. pylori* culture and antimicrobial sensitivity test, absence of comprehensive analysis of the risk factors and in the region with low levofloxacin resistance. So, more investigations are urgently needed to determine the efficacy of this regimen, especially in regions with high antibiotic resistance.

Therefore, the primary objective of this study was to determine the efficacy of the second-line LBAE regimen following failure of NBQT. The secondary objectives were to address the incidence of adverse effects and compliance. We also attempted to analyze the factors influencing eradication efficacy and investigated the effects of different patterns of antibiotic resistance on *H. pylori* eradication.

2. Patients and methods

2.1. Patients

This prospective study was conducted in the gastroenterology clinic at a tertiary hospital located in Beijing, China, between January 2013 and September 2015. Patients with dyspepsia were eligible for enrolment if their *H. pylori* infections were resistant with first-line NBQT. Previous failure was defined as a positive result of ^{13}C-urea breath test (UBT) 8–12 weeks after completion of treatment.

Patients with any one of the following criteria were excluded from the study: age younger than 18 years or older than 70 years; taking any drug that could influence the study results such as PPIs, H_2-receptor blockers, bismuth salts and antibiotics in the previous four weeks; gastrointestinal malignancy; previous gastric or esophageal surgery; severe concomitant diseases; history of allergy to any of the study drugs; currently pregnant or lactating; currently abusing alcohol or the presence of any other clinically significant medical condition that could increase the risk of adverse effects.

2.2. Methods

Patients were enrolled by the medical staff in Gastroenterology Unit after the assessment of inclusion and exclusion criteria. Before the second-line eradication therapy, all the patients were mobilized to underwent gastroscopy to assess the condition of upper digestive tract and obtain gastric mucosal biopsy for *H. pylori* culture, antimicrobial sensitivity test and cytochrome P450 isoenzyme 2C19 (CYP2C19) polymorphism analysis. All the examination and analyses were provided free of charge, and the patient was completely voluntary to decide whether to accept them. Patients deciding not to undergo gastroscopy were directly referred to LBAE therapy. The information of antibiotic resistance and CYP2C19 genotypes was used to analyze the factors influencing eradication efficacy, not to guide the selection of the second-line therapy drugs. If the second-line eradication fails, the information will be used for guiding the choice of drugs for the third-line eradication regimen. The medical staff explained the therapeutic regimen to patients in detail. Patients were informed of potential adverse effects during the treatment period and asked to return within three days after treatment to assess therapeutic compliance and determine the incidence of adverse effects. *H. pylori* eradication efficacy was determined 8–12 weeks after treatment with ^{13}C-UBT. Drugs that affected the study results were prohibited during the study. Treatment allocation was not blinded.

Adverse effects were evaluated using open-ended questions by patient self-reports. Adverse events were classified as mild (not interfering with daily routine), moderate (affecting daily routine), severe (markedly affecting the daily routine and discontinued medications) and serious (death, hospitalization, disability or require intervention to prevent permanent damage).

Compliance determined by pill counts was defined as good when $\geq$80% of the prescribed drugs was taken. Patients who took <80% of the treatment drugs were considered poorly compliant.

2.3. Ethical consideration

Written informed consent was obtained from all patients. The study was approved by the ethics committee of Peking University Third Hospital and conducted according to the principles of the Declaration of Helsinki and the standards of Good Clinical Practice.

2.4. Interventions

LBAE regimen comprised levofloxacin 500 mg once/day, bismuth potassium citrate 220 mg twice daily, amoxicillin 1000 mg twice daily and esomeprazole 20 mg twice daily for 14 days. Bismuth potassium citrate, amoxicillin and esomeprazole were administered together about 30 minutes after breakfast and dinner, and levofloxacin about 30 minutes only after breakfast.

In the first-line NBQT, sequential therapy consisted of esomeprazole 20 mg and amoxicillin 1000 mg taken twice daily for 5 days, followed by esomeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg taken twice daily for 5 days. Concomitant therapy consisted of esomeprazole 20 mg, amoxicillin 1000 mg, clarithromycin 500 mg and tinidazole 500 mg all twice daily for 10 days. Hybrid therapy consisted of esomeprazole 20 mg and amoxicillin 1000 mg taken twice daily for 14 days, supplemented with clarithromycin 500 mg and tinidazole 500 mg twice daily for the final 7 days.

2.5. H. pylori *detection*

A ^{13}C-UBT (UCBT Kit, Atom High Tech, Beijing, China) was used to confirm the presence of *H. pylori* infection 8–12 weeks after treatment. *H. pylori* infection was considered eradicated if the result of ^{13}C-UBT was negative. PPIs, H_2-receptor blockers, bismuth salts or antibiotics were discontinued for at least four weeks before ^{13}C-UBT was performed. ^{13}C-UBT is performed after an overnight fast. A baseline breath sample is obtained by blowing through a disposable plastic straw into a 20 ml container, and a capsule containing 75 mg of ^{13}C-urea is given to patients with 100 ml water. Another breath sample is collected 30 min later. The test is considered positive if the difference between the baseline sample and the 30-min sample exceeds 4.0 parts/1000 of $^{13}CO_2$ analyzed using the gas isotope ratio mass spectrometer (GIRMSZC-202, Wan Yi Sci & Tech, Anhui, China).