The Effectiveness of Sequential Therapy for Non-Ulcer Dyspepsia Patients with *H. Pylori* Infection

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Abstract

Antimicrobial resistance has decreased PPI-based triple therapy for eradication of *H. pylori.* The failure rate is almost one quarter of patients with *H. pylori* infection. The objective of this study was to assess the eradication rate and acceptance of sequential therapy for patients with non-ulcer dyspepsia (NUD). From February 2005 to May 2009, we enrolled 174 patients (Female: 62%; Age: 50.3±10.5 yr) with investigated (EGD or UGI series) NUD. Each patient adopted a 10-day sequential regimen consisting of 40 mg of pantoprazole, 1 g of amoxicillin twice daily for the first 5 days followed by 40 mg of pantoprazole, 500 mg of clarithromycin, and 500 mg of tinidazole twice daily for the remaining 5 days. Eradication was confirmed at least two months after completion of treatment by means of UBT, rapid urease test or histology. Eradication rates were calculated per-protocol and by intention-to-treat. We also used multiple regression models to assess the relationship between age, gender and success rate of eradication. Eradication was achieved in 138 out of 152 who returned for a follow-up test. Thus, the per-protocol cure rate was 90.8 %, while intention-to-treat eradication rate was relatively low at 80.2 %. Sequential therapy has proven effective in treating ulcer-related H. pylori infection in Southern Europe. In this study, sequential therapy proved effective and well-tolerated for ethnic Chinese NUD patients as well. (J Intern Med Taiwan 2010; 21: 125-132)

Key Words：*H. pylori*, Sequential therapy, Non-ulcer dyspepsia

Introduction

H. pylori infection is one of the most common infections worldwide. The bacterium causes peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. The treatment of *H. pylori* remains a challenging clinical problem since the discovery of *H. pylori* despite extensive research over the last 25 years. Increasing antibiotic resistance is a major factor for treatment failure, both for new patients and for those already treated unsuccessfully for the infection.

The Maastricht II Consensus Report agreed that effective treatment for *H. pylori* should achieve an intention-to-treat (ITT) eradication rate of over

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80%[1]. Proton pump inhibitor (PPI)-based triple therapy has been the first-line treatment of choice for over a decade. The traditional first-line treatment is a PPI (twice a day), amoxicillin (1 g twice a day), and clarithromycin (500 mg twice a day) or metronidazole (500 mg twice a day) for 7 days, i.e. three drugs twice a day for 1 week. This regime was still recommended at the Maastricht III Consensus Conference held in 2005 and in the recently published report[2]. In fact, in the use of a triple therapy that includes clarithromycin, it should only be prescribed in those locations where resistance to this specific antibiotic is under 15 to 20% of the strains.

However, in clinical practice, eradication rates are lower than 80% for many of the standard treatment regimes. The widespread and sometimes indiscriminate use of antibiotics in developing countries has resulted in a prevalence of resistance higher than in industrialized countries[3]. In the USA, clarithromycin resistance rates have a prevalence of 10-12.5%[4,5]. In Europe, there is a significant difference between clarithromycin resistance rates in Northern, Eastern, and Southern Europe, with resistance rates of 4.2%, 9.3%, and 18%, respectively[6].

In view of the decreased effectiveness of standard treatment regimens, a number of facotrs such as duration of treatment, choice of antibiotics, new drug combination, improved patient compliance, and novel agents may help to improve eradication rates. One of the important regimens, sequential therapy, consisting of proton pump inhibitor, 1 g of amoxicillin, each administered twice daily for the first 5 days followed by 40 mg of pantoprazole, 500 mg of clarithromycin, and 500 mg of tinidazole, each administered twice daily for the remaining 5 days. Sequential therapy is a novel therapeutic approach based on a different combination of the available antibiotics, and more than 2000 patients have been treated with such a therapy[7,8]. Moreover, the sequential regimen has achieved an eradication rate consistently higher than 90% by ITT analysis. It is also the only therapeutic regimen that has been proven to be superior to triple therapies in large, multicenter, randomized trials. For patients with non-ulcer dyspepsia (NUD), cure rates have been equal or less effective than for ulcer patients[9,10].

However, most of the studies published so far are *H. pylori* infection associated with peptic ulcer disease and collected in Southern Europe (Italy and Spain)[11,12], which may not apply to non-ulcer dyspepsia and lack generalization to local practice. Studies that validate this effective regimen require further investigation in the Chinese population before the regimen can be widely recommended in clinical practice. We therefore decided to evaluate the effectiveness of the sequential therapy in our area using a pilot study under clinical practice conditions, and to assess patients' adherence to this therapeutic regimen and its side effects profile.

Materials and Methods

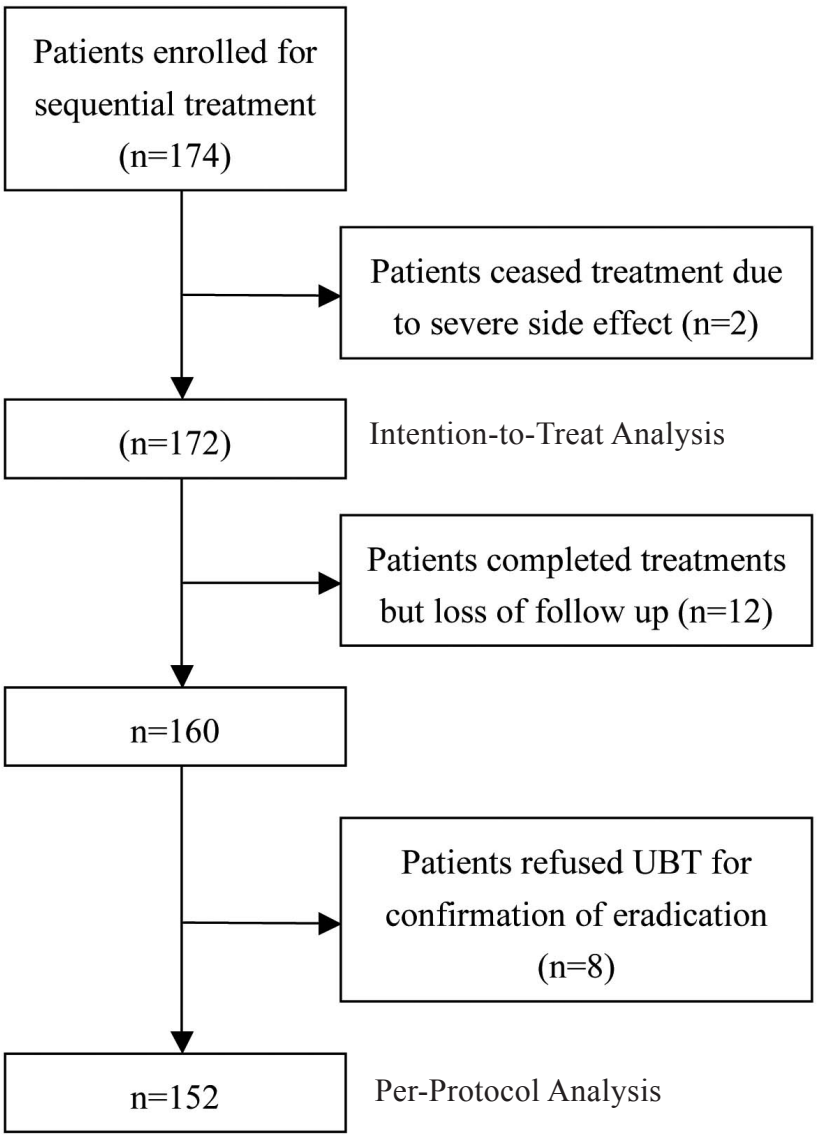
Design Overview

This was a prospective study with intention-to-treat and per-protocol analysis of eradication rate. Written informed consent was obtained from all patients. The study was performed according to good clinical practice and the Declaration of Helsinki. Study protocol was approved by the ethics institutional review board of our hospital.

Settings and Participants

Between February 2005 and December 2008, patients with investigated (either esophagogastroduodenoscopy or upper gastrointestinal series) non-ulcer dyspepsia, who were at least 18 years of age, and who had never received treatment for *H. pylori* infection, were enrolled from the outpatient department in one medical center in Taipei, Taiwan with exclusion criteria: (a) use of antibiotics, bismuth salts or nonsteroidal anti-inflammatory

Fig.1



drugs during the previous two weeks; (b) severe or unstable cardiovascular, pulmonary, or endocrine disease; (c) clinically significant renal or hepatic disease or dysfunction; (d) documented allergy to any of the antibiotics used in sequential therapy; (e) pregnancy.

We adopted a 10-day sequential regimen consisting of 40 mg of pantoprazole, 1 g of amoxicillin, each administered twice daily for the first 5 days followed by 40 mg of pantoprazole, 500 mg of clarithromycin, and 500 mg of tinidazole, each administered twice daily for the remaining 5 days.

H. pylori infection at entry was determined by at least one of the following tests: urea breath test, histology or rapid urease test. Eradication was evaluated by the urea breath test with one exception, a patient who had persistent dyspepsia and underwent a second endoscopy to rule out gastric ulcer or gastric cancer and was thus assessed

Table 1. Patients with self-reported adverse events during sequential therapy

	No. (%)
Taste alteration	48 (27.6%)
Diarrhea	10 (5.7%)
Epigastric pain	12 (6.9%)
Skin rash	2 (1.1%)
Total	72 (41.4%)

by histology. Urea breath tests (UBT) were done after an overnight fast. A baseline breath sample was obtained, and 75 mg of ^{13}C urea with citric acid (1.5 g) was administered as an aqueous solution. The results of the test were considered positive if the difference between the baseline sample and the 30-minute sample exceeded 4.5 parts per mil of $^{13}CO2$. The sensitivity and specificity values of UBT were reported as 94.7% and 95.7%, respectively[13]. This diagnostic test was performed at least 2 months after completion of treatment. Therapy compliance and side effects were assessed by personal interview after the end of antibiotic treatment.

Measurements and Outcomes

The present trial was designed as a superiority study. To show a statistically significant difference in eradication rate between an average 80% in the standard triple therapy[14] and 90% expected ITT cure rate assumed in the sequential group, a sample size of 108 patients was estimated (α = 0.05, power = 0.80). The overall eradication rates and their 95% confidence intervals were obtained by ITT and per protocol. Quantitative variables were given as means ± SD, and a univariate analysis including age and sex was performed. P-values lower than 0.05 were considered significant. All calculations were performed using STATA 9.0 software.

Results

Patients

One hundred eighty-seven patients were initially included in the study. Figure 1 shows the flow of patients through the study. Of the 174 patients who enrolled and started sequential treatment, 2 were excluded after initiation of treatment due to severe skin rash. Twenty patients were excluded from the per-protocol analysis (12 were lost to follow-up and 8 refused UBT confirmation of eradication after completion of sequential therapy). Thus, 172 patients were included in the modified intention-to-treat analysis and 152 in the per-protocol analysis (Figure 1).

Eradication of *H. pylori* Infection

H. pylori infection was eradicated in 138 of the 152 patients who returned for follow-up testing. The eradication rates confirmed after sequential treatment were 90.8% (95% CI 81%-99%) per protocol and 80.2% (95%CI: 70%-95%) in the ITT analysis. We also considered factors such as age and sex that influence the efficacy of therapy in a univariate analysis. Neither gender (88.7% cure in women vs. 92.1% in men, P = 0.9) nor age (P = 0.9) is a significant factor in sequential therapy eradication rates. Multivariate analysis was also performed and did not reach statistical significance.

Adverse Events

Of total 174 patients enrolled in this study, over 98% of the patients reported 100% adherence to the treatment. Only 2 patients discontinued treatment due to skin rash, an allergic reaction to amoxicillin. A total of 72 (41.4%) patients who received sequential therapy reported minor side effects but still completed the whole sequential treatment. The most frequent side effects were taste disturbance (mainly metallic taste) and mild diarrhea.(Table 1)

Cost Calculations

The cost of sequential treatment was estimated by the reimbursable cost of medication set by the Taiwan Bureau of National Health Insurance. The reimbursed costs of the medications in Taiwan are as follows: 1g of amoxicillin, $0.10; 500 mg of clarithromycin, $1.70; 500 mg of tinidazole, $0.10; and 40 mg of pantoprazole, $1.20. The calculated

costs for 10-day sequential therapy were $43.00 (NT: 1420), which is a little bit more expensive than standard triple therapy ($42.00, NT: 1390) and less expensive than prolonged 14 day triple therapy or quadruple therapy.

Discussion

Primary care physicians and gastroenterologists both in the United States and worldwide commonly prescribe 7-day triple therapy with a proton-pump inhibitor, clarithromycin, and either amoxicillin or metronidazole to cure *H. pylori* infection[15-18]. The PPI based triple therapy is the current first choice treatment for the eradication of *H. pylori*, but the eradication failure rate can be more than 20%. Causes of treatment failure include antibiotic resistance, poor compliance, drug-related side effects, bacterial load in the stomach, CagA status, smoking habit and gastroduodenal pathology[19]. To improve the efficacy of triple therapy in those areas with ＞15-20% primary clarithromycin resistance, many researchers and clinicians suggest the use of 14-day regimen or a 10-14 days quadruple therapy, which has been recently proposed in the updated European guidelines[20]. Novel therapeutic approaches to cure *H. pylori* such as sequential treatment have been proposed and its high efficacy makes it a suitable alternative to standard triple therapy.

The mechanism underlying sequential therapy's higher efficacy over standard triple regimens remains unclear. Amoxicillin alone can eradicate *H. pylori* in about 50% of infected patients and reduce its load in the remaining cases. However, bacteria can develop efflux channels for clarithromycin, which rapidly pump the drug out of the bacteria cell, preventing the antibiotic from binding to the ribosome. In contrast, amoxicillin can destroy the wall of bacterial cells, subsequently preventing the development of efflux channels by weakening the cell wall of the bacterium, and thus increase the intracellular diffusion of the macrolide[21], with a consequent improved outcome. Therefore, amoxicillin in the initial phase of the sequential treatment could prevent the selection of secondary clarithromycin resistance and might increase the efficacy of clarithromycin in the second phase of treatment[22]. Higher effectiveness could also be due to the addition of a new drug, tinidazole, to the standard regimen. Tinidazole is similar to metronidazole but has a longer duration of action; it is licensed for use in *H. pylori* infection in the UK, although not widely used.

Many trials have demonstrated that the cure rate following the 10-day sequential treatment is significantly higher than either 7- or 10-day standard triple therapies[23-30]. A pooled data analysis has recently been reported on the efficacy of sequential therapy[31]. However, most of the studies published so far are *H. pylori* infection associated with peptic ulcer disease, found in Caucasian patients of Southern Europe, which may not apply to non-ulcer dyspepsia and lack generalization to densely-populated areas and different ethnicities as in East Asia, including Taiwan. The cure rates found in our study (90% per protocol and 80% by ITT) are slightly lower than some published studies but still showed high efficacy, similar to those reported in more recent articles.

Seventy-two patients in our study had adverse side effects, including two with allergy to amoxicillin, who stopped treatment. Although most of the side effects were minor and did not affect compliance and completion of sequential treatment, the cases reporting side effects greatly outnumber previous published studies[30-31]. The percentage of these cases, 43.9% of all patients who received sequential treatment, is high compared to an average percentage of 10% reported in other studies. This high incidence of adverse effects may be related to differing ethnicity and the use of three antibiotics in combination. Published data[23-30] for

standard triple therapy has reported a 6 to 24% incidence of adverse effects for a regimen using only two antibiotics in Taiwanese population[32-33].

Cost is a major consideration in many countries. In Taiwan, because the cost of sequential therapy is only slightly higher than that of standard triple therapy and much lower than that of prolonged 14-day triple therapy or quadruple therapy, it is an attractive alternative to both latter therapies, with a comparable eradication rate of *H. pylori*. In the US, tinidazole has recently become available and the cost of sequential therapy based on retail prices is lower than that of standard therapy.

There are some limitations in this study. First, eradication rate of ITT analysis is 80.2 %, which is lower than other published data. In our study, several factors lowered the reporting of successful outcomes: first, the patients themselves had to pay for the urea breathing test, as that confirmation of eradication was not otherwise funded; second, NUD patients generally feel much better after eradication of *H. pylori*, so there is small incentive for them to return for formal confirmation. Another limitation of this study is that the risk factors associated with treatment failure, such as clarithromycin resistance, the absence of the CagA gene, smoking habit, etc., were not analyzed.

Conclusion

Sequential treatment is an alternative to current first-line standard triple treatment for the eradication of *H. pylori*. It is well tolerated, and many published studies have reported acceptible eradication rates, exceeding 90%. In this study, the first to examine sequential treatment in a patient population of Chinese ethnicity with non-ulcer dyspepsia, we found an excellent eradication rate, though with high incidence of mild and acceptable side effects.

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接續式滅菌療法於非潰瘍性消化不良合併幽門桿菌感染病患之療效

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摘 要

抗藥性的產生使得以三合一療法爲基礎的幽門螺旋桿菌滅菌率大幅降低。感染幽門螺旋桿菌的滅菌失敗率高達四分之一。本研究的目的是評估非潰瘍性消化不良的病人接受階段療法治療的滅菌率。自2005年2月至2009年5月，我們共收集了174例（女：63%；年齡：50.0 ± 10.8歲）經上消化道攝影或上消化道內視鏡證實爲非潰瘍性消化不良。每個病人接受爲期10天的階段療法包括前五天40毫克pantoprazole，amoxicillin 1克每日兩次，接下來五天40毫克pantoprazole，clarithromycin 500毫克，tinidazole 500毫克的滅菌療程。完成治療後至少2個月後以尿素呼氣試驗、快速尿素酶試驗或組織學證實是否滅菌成功。根除率以per-protocol及 intention-to-treat來計算。我們也用多變異數回歸模型來評估年齡、性別和成功率根除之間的關係。在164個返回追蹤試驗的病患中有148人成功治癒。因此，per-protocol的治癒率爲90.2%，而intention-to-treat計算的治療根除率相對較低，爲80.2%。階段療法在南歐國家證實能有效治療幽門螺旋桿菌感染相關的消化性潰瘍。在這項研究中，階段療法證實對於台灣的消化不良患者是有效且耐受性佳的療法。