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# Increasing the duration of dual amoxicillin plus omeprazole *Helicobacter pylori* eradication to 6 weeks: a pilot study

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## Abstract

**Background—***Helicobacter pylori* infections have become increasingly difficult to treat as antimicrobial resistance has increased

**Aim—**To test the hypothesis that a 6 week dual regimen of amoxicillin 1 gm and omeprazole 20 gm therapy BID would cure at least 90% of treatment naive *H. pylori* infections.

**Methods—**This was an open label prospective pilot study in which treatment naive subjects with active *H. pylori* infection (positive by 2 tests) received dual amoxicillin 1 g and omeprazole 20 mg, B.I.D. daily for 6 weeks. Success was accessed by UBT 4 to 6 weeks later. A tentatively effective therapy was defined as a per-protocol (PP) treatment success of 90% or greater; treatment success of 80% or less was prespecified as unacceptable.

**Results—**Sixteen patients were entered (14 men 2 woman) average age 49. At 16 patients the prespecified stopping rule of 6 treatment failures was achieved (i.e., the 95% CI excluded achieving the required 90% success rate even if 50 patients were entered.. As per protocol, enrollment was stopped. PP and intention to treat treatment success were both 62.5%; 95% CI = 35 to 84%). Compliance was greater than 99%, 5 (31%) reported side effects, all mild and none that interrupted therapy.

**Conclusion—**Despite the theory and preexisting data from Japan, in the US prolonging the duration of dual amoxicillin-PPI therapy did not improve treatment outcome to 90% or greater.

### Keywords

*Helicobacter pylori*; eradication therapy; proton pump inhibitors; amoxicillin; clinical trial

## Introduction

*Helicobacter pylori* is worldwide a major human pathogen. Despite being a common bacterial pathogen susceptible to many different antimicrobial agents, the infection proved difficult to cure requiring multidrug regimens typically along with an antisecretory agent. Over the last decade, the success rates of antimicrobial therapy have fallen largely due to the emergency of resistance to many of the drugs that heretofore have been constituents of anti-*H. pylori* therapy, particularly to macrolides and nitroimidazoles and most recently to fluoroquinolones [1,2].

One explanation for the difficulty in successfully treating *H. pylori* infections is because the organism are thought to be able to enter into a “persister state” during which they do not

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multiply and thus become phenotypically resistant to antimicrobials that require active replication [3]. The concept of a population of nonreplicating (dormant) bacteria (the persister population) that survive until the therapy is stopped was first described by Bigger in 1944 [4]. Infection with *Mycobacterium tuberculosis* is a probably the best known example of this phenomenon and is responsible for the need for long duration therapy to achieve a successful result. The outcomes of currently effective multi-drug antimicrobial therapies have generally been shown to be improved by increasing the duration of therapy, e.g., from 7 to 10 to 14 days [5,6].

The outcome in PPI/amoxicillin dual therapy is duration- and dose dependent and adversely affected by smoking [7]. Dual therapy for one week achieves approximately 25% success [8] increasing, on average, to approximately 50% after 2 weeks [9]. The question whether prolonging the duration beyond 2 weeks was addressed by Tanimura et al. who randomized 175 patients to the combination of amoxicillin (1.6 g/day), omeprazole 20 mg/day for 2, 4, or 6 weeks plus the mucoprotective drug plaunotol 240 mg/day for 8 weeks [10]. The *H. pylori* eradication rate was 46.7% for 2 weeks' treatment, increasing to 83.4% for 4 weeks' treatment, and to 100% with 6 weeks' treatment [10]. Plaunotol is a “gastroprotective” agent produced from the leaves of the medicinal plant, *Croton sublyratus* Kurz and is thought to enhance the quality of ulcer healing. Although some anti-*H. pylori* activity from *in vitro* studies as been described the MIC was approximately 20 mM or 613 mg/100 mL, the doses given in the Tanimura et al. study were much lower (i.e., 80 mg t.i.d.) suggests that plaunotol had little or no direct anti-*H. pylori* activity in their experiment. This is further supported by the fact that treatment success at 2 weeks was approximately 50% which is consistent with expectations from other studies of dual therapy [9].

The aim of this study was to test the hypothesis that a 6 week dual regimen of amoxicillin 1 gm and omeprazole 20 gm therapy BID would cure at least 90% of treatment naive *H. pylori* infections.

## Methods

This was a prospective, open-label, single-center pilot study of the treatment of patients with *H. pylori* infection referred to the Digestive Disease Section, Michael E. DeBakey VA Medical Center (VAMC) in Houston, Texas. The diagnoses of active *H. pylori* infection was made based on the presence of 2 positive tests consisting of histology with Genta stain, urea breath test ($^{13}$C-UBT), rapid urease testing (Hp*fast*; CheckMed Systems, Camp Hill, PA, or anti-*H. pylori* IgG antibody positive.

Exclusion criteria included previous *H. pylori* therapy; previous surgery of the stomach such as partial gastrectomy; use of antibiotics within the preceding 14 days; regular use of bismuth compounds (>3 times per week) in the 14 days before enrollment; presence of serious medical condition(s) precluding participation or endoscopy with biopsy; use of concomitant medication(s) known to interact with study medication; presence of Zollinger-Ellison Syndrome; pregnancy or lactation; allergy to any of the study medications; contraindication(s) to the use of any of the study drugs, or participation in a clinical trial within the last 30 days. Subjects taking other medications precluding gastric biopsy such as warfarin were also excluded. Aspirin at a dose not more than 325 mg/day was permitted.

### Therapeutic regimen

Therapy consisted of 2 drugs: an acid suppressing drug (the proton pump inhibitor omeprazole) and the antibiotic, amoxicillin. The total daily doses are 2,000 mg of amoxicillin and 40 mg of the omeprazole (each given in two divided doses). Each drug (20 mg of omeprazole and 1,000 mg of amoxicillin) were at approximately 12 hour intervals for

6 weeks. Medications were provided in customized blister packs. Patients instructed to return all the empty and unused medication blister packs and compliance with treatment was assessed by pill count and history. Subjects were requested to return for visits at 3 and 6 weeks during therapy to confirm compliance and to identify possible side effects. Outcome was assessed at 4 or more weeks post-treatment by $^{13}$C-UBT. Cure was defined as a negative urea breath test. All treatment failures were given individualized anti-*H. pylori* treatments and followed up. The regimen's safety profiles were assessed in terms of adverse events, using a questionnaire administered after 3,6 and 10 weeks of treatment.

The study was approved by the local Institutional Review Boards and all subjects signed written informed consents prior to receiving the study medication.

### Statistical analyses

For this pilot study, a tentatively effective therapy was defined as a per-protocol treatment success of 90% or greater; treatment success of 80% or less was prospectively deemed unacceptable. The protocol allowed up to 60 completed subjects with actual enrollment being based on achieving a lower 90% confidence interval (CI) of 80% or greater. Stopping rules were anytime 6 failure had occurred or after 30 patients the study would stop if a cure rate of 97% [97% (29 of 30); 90% CI, 80–99%] was achieved. Stopping points after 40 patients were a 92% cure rate [37 of 40; 90% CI, 82–98%]. After 50 patients success would be defined as cure rate of 92% [45 of 50; 95% CI, 80–96%]. If 90% or greater success was not achieved, failure would be declared.

## Results

Sixteen subjects were enrolled, including 2 women and 14 men (mean age 49 years). The ethnic groups were 10 black, 4 white non-Hispanic and 2 white Hispanic. Fourteen subjects underwent endoscopy with the findings of normal stomach 9, erosive esophagitis 3, Barrett's esophagus 1, duodenal ulcer 1.

After 6 failure occurred the study was stopped according to the prespecified stopping rules. Sixteen completed the final follow up. PP and intention to treat treatment success were both 62.5%; 95% CI = 35 – 84%),. Four subjects were smokers: 2 were cured.

The presence and an *H. pylori* infection was confirmed by histology and RUT in 7 patients, histology and UBT in 5 patients, histology and *H. pylori* antibody in 2 patients, UBT and *H. pylori* antibody in 1 patient and by RUT and UBT in 1 patient. Compliance was greater than 99% (100% by pills count in 15 patients and 98.8% in one patient).

Side effects were reported by 5 patients (31%) and were generally mild, with diarrhea being the most significant (n = 3). No patients stopped treatment because of side effects (Table 1).

## Discussion

Our study was designed as a pilot study to evaluate the effectiveness of extending the duration of amoxicillin and omeprazole dual therapy for the treatment of active *H. pylori* infections from 2 to 6 weeks, We followed the protocol for the efficient identification of potentially effective therapies and thus attempted to minimize exposure to regimens that do not achieve 90% or greater success [11].

PPI plus amoxicillin therapy given twice a day for two weeks typically provides an eradication rate of approximately 50%. Amoxicillin is a preferred antibiotic in *H. pylori* treatment regimens because it is bactericidal and resistance is rare. Because resistance rarely

develops amoxicillin can generally be used as a component of second line and salvage therapies following treatment failure. This phenomenon is termed phenotypic resistance characterized by treatment failure without development of resistance. Phenotypic resistance often results from the presence of a population of nonreplicating bacteria that survive until the therapy is stopped [3,12–14]. Longer term therapy provides an environment were the antimicrobial is present when the persistent organisms oscillate between the nonreplicating and replicating state or from intracellular to extracellular environments (ie, become phenotypically susceptible). The presence of phenotypic resistance suggests that the duration of therapy utilized may be insufficient.

The approaches to overcoming phenotypic resistance include changing the environment where dormant *H. pylori* reside thus prompting them to enter the replicative state and become susceptible to the antibiotics. This is the concept behind high dose PPI plus amoxicillin therapy[15]. Another approach would be to use antimicrobials that penetrate to the sites where the persister cells reside and whose action is independent of replication. Alternatively, one can increase the duration of therapy and finally to employ several of these methods simultaneously.

Here we attempted to confirm the results of Tanimura et al. [10] by increasing the duration of therapy to 6 weeks. To maximize compliance, we administered the PPI and amoxicillin together at approximately 12 hour intervals. We failed to achieve the prespecified 90% or greater treatment success and only achieved results more in keeping with those seen after therapy lasting 14 days. The reasons why we failed to replicate the excellent results reported by Tanimura et al. are unknown [10]. As noted above, it is unlikely that an antimicrobial effect of plaunotol was responsible, although an effect on the microenvironments where the persister organism reside can not be excluded. Alternative explanations include that omeprazole was more effective as an antisecretory agent in their population possibly because of a higher frequency of low metabolizer CYP2C19 genotypes and or the presence of atrophic gastritis [15]. Nonetheless, the hypothesis that simply extending the duration of dual amoxicillin – PPI dual therapy to 6 weeks would reliably eradicate *H. pylori* was not confirmed.

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**Table 1**

Summary of side effects report

| Adverse event | Number with complaint |
|---|---|
| Diarrhea | 3 |
| Loss of appetite | 2 |
| Rash | 1 |

One patient had 2 side effects; diarrhea and loss of appetite