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High dose extended-release lansoprazole (dexlansoprazole) and amoxicillin dual therapy for *Helicobacter pylori* infections

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Abstract

Background—*Helicobacter pylori* infections have become increasingly difficult to treat.

Aim—To examine whether amoxicillin and high dose dexlansoprazole would reliably achieve an *H. pylori* eradication rate of ≥90%.

Methods—An open-label prospective pilot study of *H. pylori* eradication in treatment-naïve subjects with active H. pylori infection (positive by two tests). Therapy: amoxicillin 1 g and dexlansoprazole 120 mg each twice a day at approximately 12 hour intervals for 14 days. Success was accessed by urea breath test. An effective therapy was defined as a per-protocol treatment success of 90% or greater; treatment success of 80% or less was prespecified as an unacceptable result.

Results—After 13 subjects were entered (12 men, one woman; average age of 54 years) the prespecified stopping rule of 6 treatment failures was achieved (i.e. the 95% confidence interval excluded achieving the required 90% success rate even if the proposed study of 50 completed patients were entered) and enrollment was stopped. Per-protocol and intention-to-treat treatment success were both 53.8%; (7/13); 95% CI = 25 to 80%. Compliance was 100%. Three patients (23%) reported side-effects, all of which were mild and none interrupted therapy.

Conclusion—Theoretically, dual PPI plus amoxicillin should reliably eradicate *H. pylori* provided nearly neutral intragastric pH can be maintained. Clearly, dexlansoprazole, despite being administered at high dose and twice a day (i.e., total daily dose 240 mg), failed to achieve an intragastric milieu consistent with dual PPI plus amoxicillin therapy being an effective anti-*H. pylori* regimen.

Keywords

Helicobacter pylori; eradication therapy; proton pump inhibitors; amoxicillin; dexlansoprazole; clinical trial; smoking

Introduction

Helicobacter pylori infection is etiologically associated with gastritis, gastric atrophy, peptic ulcer and gastric cancer. There is no current antimicrobial regimen that reliably produces cure rates of 90% or greater world wide. The most common causes of treatment failure of

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regimens highly successful in some locales are a poor compliance, antimicrobial resistance, or both. Amoxicillin resistance is rarely reported and amoxicillin itself is generally well tolerated. Early studies showed that amoxicillin alone produce poor success with few infections being cured [1]. The addition of a proton pump inhibitor (PPI) provided markedly improved results and led to considerable interest in amoxicillin-PPI dual therapy [2]. However, this regimen fell into disfavor when it became evident that standard doses of this dual therapy typically provide cure rates of approximately 50% [3–5]. Theoretically however, amoxicillin is a near ideal antimicrobial as it is bacteriocidal and resistance rarely occurs despite treatment failure. It has been proposed, and there are data to support the notion that treatment failure is related to nonreplicating bacteria that survive until after therapy is stopped [6–8]. Extending the duration of dual therapy to 6 weeks proved ineffective in improving treatment success [9]. The presence of an acidic local environment has been suggested as being responsible for maintaining the bacteria in a nonreplicative state and there have been a number of studies showing that increasing the effectiveness of antisecretory therapy by increasing the dosage and/or frequency of administration or focusing on PPI slow metabolizers can result in eradication rates greater than 90% [10–17].

The introduction of an extended-release of lansoprazole suggested the possible availability of commercially available product that would allow one to easily and conveniently achieve an intense and prolonged PPI effect [18–20]. This study was designed to test whether we could achieve >90% *H. pylori* eradication using a long acting PPI plus amoxicillin for two weeks without requiring pharmacogenetic individualization of *H. pylori* eradication therapy in relation of CYP2C19 genotyping. A theoretical model of the acid suppressive effect of standard form lansoprazole suggested that the ideal dose in rapid CYP2C19 metabolizers would be approximately 180 mg twice per day [21]. We reasoned that considering the difference in half life between the standard and long acting formulations [18–20], a total daily dose of the long acting version of lansoprazole between 90 and 120 mg should be approximately equivalent to 180 mg twice a day. To avoid under dosing we administered 120 mg of dexlansoprazole twice a day (total dose 240 mg) to test the hypothesis that a 2-week dual regimen of twice a day amoxicillin and high dose long acting lansoprazole therapy would cure at least 90% of treatment-naïve *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 in Houston, Texas. The diagnosis of active *H. pylori* infection was made based on the presence of two positive tests consisting of histology with Genta stain, urea breath test (^{13}C-UBT), rapid urease testing (Hp*fast*; CheckMed Systems, Camp Hill, PA, USA) or anti-*H. pylori* immunoglobulin G antibody positive serology.

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

Therapy consisted of two drugs: an acid-suppressing drug (the proton pump inhibitor dexlansoprazole) and the antibiotic, amoxicillin. The total daily doses are 2000 mg of amoxicillin and 240 mg of dexlansoprazole (each given in two divided doses at approximately 12 hour intervals for 2 weeks). Medications were provided in customized blister packs. Patients were 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 visit at 2 weeks during therapy to confirm compliance and to identify possible side-effects. Outcome was assessed at least 4 weeks after the end of antimicrobial therapy by ^{13}C-UBT (75 mg 13C-urea and 2 grams of citric acid, Meretek Diagnostics, Rockville, MD). Cure was defined as a negative urea breath test. All treatment failures were given individualized anti-*H. pylori* treatments and followed up. All treatment failures were given individualized anti-*H. pylori* treatments and followed up. The regimens safety profiles were assessed in terms of adverse events using a questionnaire administered after 4 and 14 days of treatment [22].

The study was approved by the local institutional review boards and all subjects signed written informed consents prior to receiving the study medication.

Design and analysis

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 [23]. The protocol allowed up to 50 completed subjects with actual enrollment being based on achieving a lower 90% confidence interval (CI) of 80% or greater. Stopping rules were anytime six failures had occurred; 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 a cure rate of 92% (45 of 50; 95% CI, 80–96%). If 90% or greater success was not achieved, failure would be declared.

Results

Thirteen subjects were enrolled, including one woman and 12 men (mean age 54 years). The ethnic groups were five black, five white non-Hispanic and three Hispanic. Twelve subjects underwent endoscopy with the findings of normal stomach (n = 6), gastric erythema (n = 3), gasrtritis (n = 1), duodenitis (n = 1), and antral ulcer (n = 1).

After six failures occurred the study was stopped according to the prespecified stopping rules. Thirteen completed the final follow up. PP and intention-to-treat treatment success were 7/13 (53.8%). Seven subjects were smokers and two of these were cured of their *H. pylori* infection (failure rate 71%) compared to 1 failure among 6 nonsmokers (16.6%);

P=0.103. Even among nonsmokers the treatment success was less than 90%. Compliance was 100%.

The presence of *H. pylori* infection was confirmed by histology and UBT in eight patients, histology and rapid urease testing in two patients, histology, rapid urease test and UBT in one patient, UBT and *H. pylori* antibody in one patient and by rapid urease testing and UBT in one patient.

Side-effects were reported by three patients (23%) and were generally mild, with diarrhea being the most significant (n = 2). No patients stopped treatment because of side-effects (Table 1). One patient had taste disturbance, nausea and diarrhea, and another one had stomach pain and increase in appitite.

All treatment failures were followed up and retreated with 14 day concomitant therapy with success.

Discussion

The study was designed as a pilot study to evaluate the effectiveness of using long active PPI and amoxicillin as a dual therapy for the treatment of active *H. pylori* infections. 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 [23].

PPI plus amoxicillin therapy given twice a day for 2 weeks typically provides an eradication rate of approximately 50% [3–5]. The concept behind high dose PPI-amoxicillin therapy is to overcoming phenotypic resistance by changing the environment where dormant *H. pylori* reside causing them to enter the replicative state and become susceptible to the antibiotics. The use of a high dose long-acting lansoprazole failed to achieve 90% or greater treatment success. Because compliance has previously been shown to be a critical variable for success with dual therapy [24–26], we administered the PPI and amoxicillin together at approximately 12-h intervals and achieved 100% compliance. Possibly, administration of amoxicillin more frequently (e.g., every 6 hours) might have been more successful [27]. We and Kim et al. previously tried every 8 hours without out achieving the prespecified 90% or greater treatment success [28, 29]. Alternatively, providing the amoxicillin in a different formulation such as a suspension [25] or adding sodium bicarbonate (e.g., 1 and 3 hours after meals and at bedtime) to ensure that the pH remained 6 or above may be necessary if extended release lansoprazole is to become an effective addition to the therapeutic armamentarium in Western countries where most patients are CYP2C19 rapid metabolizers. Smoking has previously been suggested as an important factor related to treatment failure with dual therapy [30]. The primary deleterious effect of smoking in terms of gastric physiology is thought to be related to gastric secretion as smoking both increases acid secretion and decreases duodenal and pancreatic bicarbonate secretion [31–33]. Our prior studies of dual therapy have not experienced a significant decrease in effectiveness in relation to smoking [9, 28, 34] such that if smoking is important, the factor only comes into play when the attained pH is a critical variable in outcome. Studies in which intragastric pH is assessed

will be needed to address whether the ability to maintain the intragastric pH at 6 or greater is a critical factor in determining the effectiveness of dual therapy.

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Table 1

Side effects of therapy

Side effects	Number of subjects
Diarrhea	2
Nausea	1
Stomach pain	1
Taste disturbance	1
Increase in appitite	1