

THE IMPACT OF *Helicobacter pylori* RESISTANCE ON THE EFFICACY OF A SHORT COURSE PANTOPRAZOLE BASED TRIPLE THERAPY

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ABSTRACT – Background – Many of the currently used *Helicobacter pylori* eradication regimens fail to cure the infection due to either antimicrobial resistance or poor patient compliance. Those patients will remain at risk of developing potentially severe complications of peptic ulcer disease. **Aim** – We studied the impact of the antimicrobial resistance on the efficacy of a short course pantoprazole based triple therapy in a single-center pilot study. **Methods** – Forty previously untreated adult patients (age range 20 to 75 years, 14 males) infected with *Helicobacter pylori* and with inactive or healing duodenal ulcer disease were assigned in this open cohort study to 1 week twice daily treatment with pantoprazole 40 mg, plus clarithromycin 250 mg and metronidazole 400 mg. *Helicobacter pylori* was assessed at entry and 50 ± 3 days after the end of treatment by rapid urease test, culture and histology of gastric biopsies. The criteria for eradication was a negative result in the tests. Susceptibility of *Helicobacter pylori* to clarithromycin and metronidazole was determined before treatment with the disk diffusion test. **Results** – One week treatment and follow up were complete in all patients. Eradication of *Helicobacter pylori* was achieved in 35/40 patients (87.5%) and was higher in patients with nitroimidazole-susceptible strains [susceptible: 20/20 (100%), resistant: 10/15 (67%)]. There were six (15%) mild adverse events reports. **Conclusions** – A short course of pantoprazole-based triple therapy is well tolerated and effective in eradicating *Helicobacter pylori*. The baseline metronidazole resistance may be a significant limiting factor in treatment success.

HEADINGS – *Helicobacter* infections. Peptic ulcer. *Helicobacter pylori*. Anti-ulcer agents. Benzimidazoles. Sulfoxides.

INTRODUCTION

Helicobacter pylori (*Hp*) eradication dramatically reduces both duodenal and gastric ulcer recurrence⁽²⁵⁾. Several therapeutic regimens have been proposed, but identifying the ideal regime for achieving eradication has been elusive. A large number of pills needs to be taken daily, the duration of the therapy and the presence of adverse events can limit the patient compliance. Clarithromycin is the most effective single antibiotic available but frequently causes troublesome oral burning and taste disturbance⁽²⁶⁾. More recently, the triple therapy with PPIs, clarithromycin, and either a nitroimidazole (tinidazole or metronidazole) or amoxicilin has been recommended^(6, 8, 13, 14). This regimen is given twice a day, and 1 week of treatment may be as effective as 2 weeks. Per protocol, eradication rates have

generally been over 90%, the regimen is well tolerated, and it seems to have few side effects. PPIs also improve minimum inhibitory concentration values of some antibiotics and has some direct anti-*Hp* effects, factors that make combination therapies with PPIs more attractive⁽¹²⁾. However, there has been a concern about metronidazole resistance^(3, 18, 23) and more recently also about clarithromycin resistance⁽²⁹⁾, factors for reducing eradication efficacy of the therapy.

The aim of this study was to determine the influence of previous *Hp* resistance to clarithromycin and metronidazole on the efficacy of a short term triple therapy with pantoprazole, metronidazole and smaller doses of clarithromycin (250 mg, twice daily) than generally used (in an effort to limit side effects, control costs and improve patient tolerance and compliance), in a group of patients with duodenal ulcer.

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METHODS

Patients were recruited from the Gastroenterology Unit, “Hospital das Clínicas”, of the University of São Paulo, Medical School, São Paulo, SP, Brazil. The study protocol, including the informed consent, was approved by the Ethics Review Committee of the Hospital.

The inclusion criteria were: outpatients aged 18 to 75 years with previously untreated *Hp* infection and an endoscopically proven diagnosis of healed or healing duodenal ulcer and unequivocal evidence of *Hp* infection, based on two of the following tests: rapid urease test, culture and histology of gastric biopsies.

The following were considered as exclusion criteria: endoscopic evidence of active peptic ulcer and ulcer complications, signs or symptoms suggesting gastrinoma; erosive reflux esophagitis, esophageal strictures, previous esophagus and/or gastrointestinal tract surgery except appendectomy, cholecystectomy and polypectomy, severe concurrent illnesses; ingestion of substituted benzimidazoles for 3 days up to 30 days before inclusion; chronic use of steroidal or non-steroidal antiinflammatory drugs; simultaneous intake of drugs whose absorption is pH dependent; concurrent use of any medication that could interact with any of the study drugs; previous hypersensitivity to any of the trial drugs; alcohol or drug abuse, pregnancy or breast-feeding periods; women of child-bearing potential not using any effective contraceptive method; clinically relevant deviations from the normal range in laboratory parameters; patients whose compliance with the trial could be doubtful and patients who had participated in any clinical study up to two months before inclusion.

Eligible patients were assigned in this open, cohort study to a triple therapy, consisting of 7 days pantoprazole 40 mg, clarithromycin 250 mg and metronidazole 400 mg administered bid. Patients were all warned to avoid alcohol and to pay attention to potential adverse events such as taste disturbance, nausea, or loose stools. Patients were encouraged to complete the use of the medications provided and were informed that successful completion of treatment would offer a great chance of eradication success. The patients were scheduled for three visits: pre-treatment, 7 days and 50 ± 3 days after the treatment (Table 1).

Pre-treatment evaluation included patient’s medical history, recording pertinent data such as smoking and drinking habits, drug use and frequency, presence and severity of epigastric pain, nausea, vomiting, heartburn, regurgitation, eructation of air or hypersalivation.

The symptoms were scored according to the severity as follows: score 1 was attributed to **mild** symptoms (mild discomfort, not interfering with usual activities); score 2 to **moderate** symptoms (distressing symptoms, partly interfering with usual activities) and score 3 to **severe** symptoms (markedly distressing symptoms, impairing usual activities).

TABLE 1 – Study schedule

	Visit 0	Visit 1	Visit 2
	Baseline	Day 7	Day 50 ± 3
Patient information/consent	X	—	—
Medical history	X	—	—
Inclusion/exclusion criteria	X	—	—
Physical examination	X	—	X
Endoscopy/biopsies	X	—	X
Clinical symptoms	X	X	X
Laboratory investigation	X	—	X
Compliance control	—	X	—
Adverse events	—	X	X

Physical examination was also performed. This routine was repeated at each subsequent follow-up visit, in addition to drug intake monitoring and careful investigation of the adverse events.

Before treatment, screening blood tests were taken, including hemoglobin, white blood cell count, blood glucose, potassium, creatinine, asparagine transaminase, alanine transaminase, bilirubin, and alkaline phosphatase. Endoscopy with biopsies to confirm *Hp* infection and determination of the susceptibility of *Hp* isolates to clarithromycin and metronidazole were done in all included patients.

As per protocol, patients were seen 1 week after starting the medication to check compliance and adverse events.

After the end of drug treatment, 50 ± 3 days, the patients returned for a new clinical evaluation, blood tests and repeat endoscopy (with rapid urease test, culture and histology) to determine *Hp* eradication.

Hp diagnosis

At each endoscopic examination, 12 biopsies (6 from the antrum and 6 from the corpus) were taken to assess *Hp* status. Four biopsies (two from the antrum and two from the corpus) were used for the rapid urease test, which was performed with a commercially available urease test kit. Four biopsies (two from the antrum and two from the corpus) were fixed in neutral buffered 10% formalin and used for histological evaluation of *Hp*. Biopsy specimens were processed, embedded in paraffin, cut in sequential 4-µm sections, and stained with hematoxylin-eosin and Giemsa. Four biopsies (two from the antrum and two from the corpus) were used for the culture.

Biopsies from the corpus were taken because antimicrobial combinations including pantoprazole may shift *Hp* in the antrum to the corpus⁽²⁴⁾. Eradication was defined as the condition which there is no evidence of presence *Hp* in the tests (urease, histology and culture) 7 weeks after cessation of the antimicrobial therapy.

Antimicrobial resistance

For the testing of antimicrobial resistance, the susceptibility of *Hp* isolates to clarithromycin and metronidazole was determined with the disk diffusion test. Susceptibility tests were performed on Mueller-Hinton agar plates, supplemented with 5% horse blood. Single plates, which had been predried at 35 °C for 1 hour, were used for each disk.

All isolates were tested by disk diffusion for clarithromycin (15 µg) and metronidazole (5,0 µg). The tests consisted of making a standard inoculum of fresh *Hp* culture in Brain Heart Infusion broth to a 1 McFarland equivalent, inoculating each plate by gently swabbing in three directions and after placement of the disk incubating microaerobically for 72 h at 35 °C. Isolates showing scattered colonies within the zones of inhibition were recorded as resistant.

Three interpretive categories of susceptibility results were defined; strains with inhibitory zone diameters of more than 26 mm were defined as susceptible, strains with zone diameters of 20 to 26 mm were deemed intermediate, and those with zone diameters of less than 20 mm were deemed resistant^(21, 30).

Sample size determination

Triple therapy with pantoprazole, clarithromycin, and metronidazole was estimated to eradicate 90%. With 80% power to detect a true difference between treatment regimens efficacy, with similar population characteristics at a significance level of $P < 0.05$, it was estimated that 26 patients were necessary. Assuming a 20% drop out rate, this meant that a minimum of 31 patients had to be included in the study.

Statistical analysis

Descriptive analysis consisted of calculation of absolute and relative frequencies for qualitative variables, and mean and standard deviation (SD) for quantitative variables. All patients selected were included in a conservative intent-to-treat (ITT) analysis, in which all patients without final *Hp* determination or with protocol violations would be considered treatment failures. In the per protocol analysis, patients who either dropped out because of adverse events or protocol violations would be excluded.

The influence of demographic and clinical parameters on the eradication rates was analyzed by the t of Student test. The score sums for the symptoms before and after the treatment were compared by means of the Friedman-test. The *Hp* status, before and after the treatment, were compared by means of the Signal test and the influence of primary antimicrobial resistance on the eradication rates by the Fisher test.

RESULTS

A total of 40 patients were included in the study. Demographic data is shown in Table 2.

TABLE 2 – Demographic data of patients treated with the PCM* regimen

Parameters	Values
No. of patients	40
Male:female ratio	14:26
Age (yr) *	46.6 ± 15.0; 20-75**
Smokers (%)	10
Alcohol (%)	0
Weight (kg)	67.0 ± 15.0; 43-108**
Height (cm)	162.3 ± 11.4; 130-190**

*PCM: pantoprazole + clarithromycin + metronidazole

**Values expressed as mean ± SD; range

The patient's medical data such as sex, age, smoking and drinking habits, did not influence the eradication rates.

The presence and severity of dyspeptic symptoms (epigastric pain, heartburn, burning and nausea) significantly decreased during the treatment period ($P < 0.001$ Friedman's test).

There was no dropout or protocol violation. Final *Hp* status was assessed in all patients.

The *Hp* eradication rate was 87.5% (35/40). *Hp* colonies were not isolated in cultures making it impossible to perform the antimicrobial resistance test in 5 out of 40 patients. Metronidazole resistant (MR) strains were found in 43% of the remaining 35 patients and the therapy failed in 5 of them (33%). Eradication of *Hp* was significantly higher in patients with nitroimidazole-susceptible strains [susceptible: 20/20 (100%), resistant: 10/15 (67%), $P < 0.01$]. There were no clarithromycin resistant (CR) strains.

There were six (15%) mild adverse events reports possible related to the medications of the study. Four patients complained of taste disturbances (10%); three of them of bitter taste and one of metallic taste. One patient reported nausea (2.5%) and one hypersalivation (2.5%).

Compliance with medications as assessed by pill counts was very high. All patients took all of their pills. Laboratory hematologic parameters assessed did not change significantly with drug therapy.

DISCUSSION

No direct correlation between resistance and eradication failure has been found in most studies of proton-pump inhibitor (PPI) triple therapy, in which either amoxicillin or clarithromycin is used as the

second antibiotic with metronidazole^(3, 18, 23, 29). Clarithromycin resistance is still low in most communities. Current data are scarce, but indicate that when present it has a higher negative impact on treatment outcome than metronidazole resistance. Resistance frequently emerges with treatment failure, although it is not clear as to what extent resistant organisms will spread.

The cure rate with most regimens dropped significantly, in the case of nitroimidazole-resistant strains, compared to nitroimidazole-susceptible strains. In our study, the eradication rate (87.5%), was similar to the ones reported by other authors^(1, 2, 4, 13, 15, 16, 22) and the metronidazole resistance influenced the therapy outcome in 14.3% of the patients. The higher rates of metronidazole resistance in Brazil can be due its widespread use in gynecological infections and parasitic diseases like giardiasis and amebiasis⁽²⁷⁾.

In a review of all available data in the literature including 770 study-arms, HOUBEN et al.⁽¹⁰⁾ observed that in the case of nitroimidazole resistance, a drop in efficacy of up to 50% was found for bismuth-based triple and proton pump inhibitor-based triple therapies.

However, in a recent German study with 93 patients⁽⁷⁾, the antimicrobial resistance did not influence the efficacy of a 7-day regimen with pantoprazole (40 mg twice daily), metronidazole (500 mg twice daily), and clarithromycin (250 mg twice daily). Primary metronidazole resistance was found in 14 of them (22.9%), but only one did not respond to the therapy.

YOUSFI et al.⁽³²⁾ also did not find that metronidazole resistance predicted treatment failure in their study.

Those contradictory results indicated that the influence of the nitroimidazole resistance on the PPI based triple therapy outcome depends also on other factors like duration of therapy or the nature of second antibiotic used in the association.

Combination regimens with high-dose clarithromycin are costly, require many tablets per day, and adverse events such as diarrhea and taste perversion are frequently associated. Moreover, caution is required when using the 1.5 g/day dosage owing to the risk of severe, life-threatening pseudomembranous colitis, particularly in the elderly⁽²⁸⁾. One-week low-dose clarithromycin (250 mg bid) combinations with PPIs and tinidazole or metronidazole have also been tested and have achieved impressive (93%-95%) eradication rates^(10, 15, 16). However, the 30%-40% prevalence of metronidazole-resistant *Hp* strains in the United Kingdom, Belgium, Finland, and

other industrialized countries^(9, 17, 31) casts doubt on the reproducibility of such results in the general population. Indeed, two other studies from Canada and Ireland, using similar regimens, achieved eradication rates of only 81.5% and 78.9%, respectively^(5, 9, 31).

A meta-analysis of 82 studies involving 110 treatment arms and 6,123 patients undertaken by HUANG et al.⁽¹¹⁾ reviewed the importance of clarithromycin dose in the triple therapy based on PPI. The pooled eradication rate in patients treated with a PPI + metronidazole and clarithromycin 500 mg bid was 90.8% (95% CI: 87.0%-94.5%) compared to 88.5% (95% CI: 85.5%-91.5%) in patients treated with clarithromycin 250 mg bid by per protocol analysis ($P = 0.082$). The corresponding rates by intention-to-treat analysis for clarithromycin 500 mg bid. and 250 mg bid. was 88.3% and 86.7%, respectively ($P = 0.25$). Although the authors concluded that clarithromycin 500 mg bid should be used in these combinations to achieve the best first treatment results, significant difference was observed only when clarithromycin was associated with amoxicillin but not with metronidazole.

More recently, the large MACH-2 trial also used a lower dose of clarithromycin in the clarithromycin and metronidazole combination (250 mg instead of 500 mg)⁽¹⁹⁾. Compared to our results, the overall rate of resistance to clarithromycin was higher (none vs. 3%) but the resistance to metronidazole was found to be lower (43% vs. 24%). There was a 15% decrease in the success rate with omeprazole-metronidazole-clarithromycin treatment (from 91% to 76%) for metronidazole-resistant strains. This decrease was also higher (from 100% to 67%) for metronidazole-resistant strains in our study. The lower eradication rate suggests that baseline metronidazole resistance may be a significant limiting factor in treatment success.

Our results concerning the resistance to clarithromycin match the low rates observed by MENDONÇA et al. (7%)⁽²⁰⁾.

Therapy failure secondary to antibiotic resistance is understandable, but treatment failure with the organisms remaining susceptible to the antibiotics posttherapy also occurs, although it was not observed in our study.

The results indicate that *Hp* antimicrobial resistance is relevant to the success of eradication. The high MR but low CR prevalence among *Hp* isolates in this study suggests that PPI-based triple therapy including amoxicillin and clarithromycin may achieve the most favorable eradication rate.

Eisig JN, André SB, Silva FM, Hashimoto C, Moraes-Filho JPP, Laudanna AA. O impacto da resistência do *Helicobacter pylori* na eficácia de um esquema tríptico a curto prazo com pantoprazol. Arq Gastroenterol 2003;40(1):55-60.

RESUMO – Objetivo – Vários esquemas utilizados na erradicação do *Helicobacter pylori* falham por resistência ao antibiótico ou por pouca aderência ao tratamento pelo paciente. Esses pacientes permanecerão com alto risco de desenvolver complicações decorrentes da úlcera péptica. Assim, estudou-se o impacto da resistência antimicrobiana na eficácia de esquema tríptico em um único centro. **Métodos** – Quarenta pacientes, virgens de tratamento para erradicação da bactéria (idade entre 20 e 75 anos, 14 homens) infectados pelo *Helicobacter pylori* e com úlcera duodenal ativa ou em cicatrização foram avaliados em um estudo aberto durante 1 semana com esquema de tratamento constituído por pantoprazol 40 mg, claritromicina 250 mg e metronidazol 400 mg, todos administrados duas vezes ao dia. A presença do *Helicobacter pylori* foi analisada no início e entre 50 ± 3 dias após o final do tratamento, pelo teste rápido da urease, cultura e histologia, obtidos através de biopsias gástricas. O critério de erradicação foi o resultado negativo em todos os testes. A susceptibilidade da claritromicina e metronidazol foi determinada antes do tratamento pelo teste de disco difusão em agar. **Resultados** – O tratamento e o seguimento foi completo em todos os pacientes. A erradicação do *Helicobacter pylori* foi verificada em 35/40 pacientes (87,5%) e foi maior nos pacientes com cepas susceptíveis ao nitroimidazólico (susceptíveis 20/20 (100%), resistentes 10/15 (67%)). Seis pacientes (15%) referiram sintomas adversos leves. **Conclusões** – O esquema tríptico a curto prazo com pantoprazol é bem tolerado e efetivo na erradicação do *Helicobacter pylori*. A resistência ao metronidazol pode ser fator limitante significativo no sucesso terapêutico.

DESCRIPTORIOS – Infecções por helicobacter. Úlcera péptica. *Helicobacter pylori*. Antiulcerosos. Benzimidazóis. Sulfóxidos.

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