Helicobacter pylori ERADICATION USING TETRACYCLINE AND FURAZOLIDONE VERSUS AMOXICILLIN AND AZITHROMYCIN IN LANSOPRAZOLE BASED TRIPLE THERAPY: an open randomized clinical trial

Laura Cidrão **FROTA**[1], Maria do Perpétuo Socorro Saldanha da **CUNHA**[2], Carlos René Lima **LUZ**[1], Antonio Haroldo de **ARAUJO-FILHO**[1], Luciano A. S. **FROTA**[1] and Lucia Libanez Bessa Campelo **BRAGA**[1]

ABSTRACT - ***Background -*** Optimal anti-*Helicobacter pylori* treatment has not yet been established. ***Aim*** - To evaluate *H. pylori* eradication using tetracycline and furazolidone versus amoxicillin and azithromycin in lansoprazole based triple therapy in northeastern of Brazil. ***Patients and methods -*** One hundred and four patients with *H. pylori* infection, as determined by rapid urease testing and histology, were randomly assigned to receive either: lansoprazole (30 mg *q.d.),* tetracycline (500 mg *q.i.d.),* and furazolidone (200 mg *t.i.d.)* for 7 days (LTF; n = 52); or lansoprazole (30 mg *b.i.d.)* and amoxicillin (1 g *b.i.d.)* for 1 week, plus azithromycin (500 mg *q.d.)* for the first 3 days (LAAz; n = 52). *H. pylori* eradication was assessed 3 months following completion of therapy by means of rapid urease testing, histology and a ^{14}C-urea breath test. ***Results -*** *H. pylori* eradication was achieved in 46 of 52 (88.4%, 95% CI: 77.5%-95.1%) patients in LTF group and in 14 of 52 (26.9%, 95% CI: 16.2%-40,1%) patients in LAAz group. On a per-protocol analysis, eradication rates were 91.8% (95% CI: 81.4%-97.3%) and 28.5% (95% CI: 17.2%-42.3%), respectively in LTF and LAAz groups. ***Conclusion*** - The LAAz regimen yielded unacceptably low eradication rates. On the other hand, the LTF scheme represents a suitable alternative for *H. pylori* eradication.

HEADINGS – *Helicobacter pylori*. *Helicobacter* infections, chemotherapy. Tetracycline. Furazolidone. Amoxicillin. Azithromycin. Proton pumps, antagonists & inhibitors.

INTRODUCTION

Over the past decade, anti-*H. pylori* therapy has undergone a remarkable evolution. However, optimal treatment has not yet been established, especially in developing countries where such positive results as those reported overseas have not been reproduced.

The standard therapeutic regimen currently available consists of an association of a proton-pump inhibitor (PPI) and clarithromycin with either amoxicillin or nitroimidazoles[26, 28]. However, bacterial resistance to nitroimidazoles and increasing resistance to clarithromycin has prompted the search for alternative therapies. Besides that, the optimal regimen strongly depends on many local variables. A regimen useful in one geographical area may not be effective or practical in another area. The issue of cost further complicates the choice, especially in developing and underdeveloped countries.

Department of [1]Internal Medicina; [2]Department of Pathology, Federal University of Ceará, Walter Cantídeo University Hospital, Fortaleza, CE, Brazil.
Address for correspondence: Dr. Lucia L. Braga - Department of Internal Medicine - Federal University of Ceará - Prof. Costa Mendes, 1608, 4th floor - Rodolfo Teófilo - 60430-140 - Fortaleza, CE, Brazil. Email: lucialib@terra.com.br

Furazolidone is a poorly absorbed antimicrobial agent that is both available and inexpensive in developing countries. In recent years, a number of clinical trials performed with furazolidone have proven its suitable anti-*H. pylori* activity. To date, resistance to tetracycline and furazolidone seems to be rare[13, 23, 24].

Azithromycin is a potentially attractive agent for *H. pylori* eradication given its excellent inhibitory concentration for this organism and long biologic half-life[4, 16]. However, clinical trials with azithromycin have displayed considerable variation with respect to the regimens used and the results obtained. Eradication rates varying between 93% and 22% have been reported[1, 3, 8, 20, 29, 31]. In Brazil, few clinical trials have evaluated the role of azithromycin and furazolidone in the treatment of *H. pylori* infection and most of them have been performed in southeastern of the country[8, 28]. Since Brazil is a country with continental dimension regional differences are likely to occur.

The aim of this randomized open trial is to evaluate *H. pylori* eradication using tetracycline and furazolidone versus amoxicillin and azithromycin in lansoprazole based triple therapy in northeastern of Brazil.

MATERIALS AND METHODS

Patient selection

Dyspeptic patients attending the Division of Gastroenterology of the "Walter Cantídeo" University Hospital (HUWC, Federal University of Ceará, Brazil) with endoscopic diagnoses of peptic ulcer or non-ulcer dyspepsia were invited to participate in the study. Inclusion criteria consisted of *H. pylori* infection, as determined by rapid urease test (RUT) and confirmed by histological examination, age between 18 and 75 years, inclusive, and written informed consent. Exclusion criteria were as follows: previous anti-*H. pylori* therapy, pregnancy

TABLE 1 - Demographic and clinical characteristics of study patients

	LAAz	LTF	Significance (*P*)
Number of patients	52	52	
Male/female ratio	27/25	25/27	NS
Mean age (SD), years	40 (11)	42 (12)	NS
Smoking habits [n (%)]			
Non-smokers	35 (53.0%)	31 (46.9%)	NS
< =10 cigarettes/day	04 (33.3%)	08 (66.6%)	NS
>10 cigarettes/day	13 (50.0%)	13 (50.0%)	NS
Endoscopic diagnosis [n (%)]			
Duodenal ulcer	37 (49.3%)	38 (50.67%)	NS
Gastric ulcer	4 (80.0%)	1 (20.0%)	NS
Gastric and duodenal ulcers	4 (57.1%)	3 (42.86%)	NS
Gastritis/duodenitis	7 (41.1%)	10 (58.82%)	NS

LAAz: lansoprazole, amoxicillin and azithromycin
LTF: lansoprazole, tetracycline and furazolidone

TABLE 2 - Compliance and side effects observed in the study groups

	LAAz (n = 52)	LTF (n = 52)	Significance (*P*)
Compliance of medication [n(%)]			
Full	49(94.2%)	40 (76.9%)	NS
80-99%	2(3.8%)	10(19.2%)	NS
70-79%	1(1.9%)*	1(1.9%)**	NS
<70%	0	1(1.9%)***	NS
Severity of side-effects [n(%)]			
None	29(55.7%)	21(40.3%)	NS
Slight	23(44.2%)	28(53.8%)	NS
Mild	4(7.6%)	17(32.6%)	NS
Moderate	2(3.8%)	3(5.7%)	NS
Severe	0	1(1.9%)	NS
Symptoms of side-effects [n(%)]			
Diarrhea	17(32,6%)	2(3,8%)	*P*<0,0001
Nausea	5(9,6%)	18(34,6%)	*P*=0,004
Anorexia	-	8(15,3%)	*P*=0,006
Dizziness	1(1,9%)	10(19,2%)	*P*=0,008
Taste disturbance	-	3(5,7%)	NS
Headache	3(5,7%)	6(11,5%)	NS
Pruritus	2(3,8%)	2(3,8%)	NS
Epigastric pain	1(1,9%)	-	NS

* Amoxicillin:75%; **Furazolidone:71.5%; ***Therapy discontinuation (tetracycline:64.3%; furazolidone: 33.3%)

or lactation, gastric surgery (except highly selective vagotomy or oversewing of ulcer perforation), malignancy, severe liver or kidney disease, known or suspected hypersensitivity to the medication used in the study, chronic alcoholism, and suspected lack of compliance, and patients who had previously undergone eradication therapy. These criteria were ascertained by taking a complete history, physical examination, and appropriate hematologic and biochemical tests. The study was approved by the local Ethics Committee.

One hundred and four subjects were selected. Patients' clinical and demographic characteristics are listed in Table 1. None of the differences are significant.

Upper gastrointestinal endoscopy was performed (Pentax EG 2901 videoscope, Japan), and eight gastric biopsies were taken to assess *H. pylori* status (four from the antrum and four from the corpus). Endoscopic and biopsy forceps were thoroughly cleaned with an enzymatic detergent and disinfected with 2% glutaraldehyde between all procedures. Four specimens (two from both antrum and corpus) were used for RUT, which was performed with a commercially available kit (Laboclin, Minas Gerais, Brazil).

Histologic assessment of *H. pylori* status was performed using further four biopsy specimens (hematoxylin–eosin and Giemsa stain), two from the antrum, and two from the gastric body. *H. pylori* infection was defined when positive results in both the rapid urease test and histology were obtained.

Study design

Patients were randomized to receive either: 1) lansoprazole (capsules, Medley, São Paulo, Brazil), 30 mg *b.i.d.* (before breakfast and dinner), plus amoxicillin (capsules, Aché, São Paulo), 1 g *b.i.d.* (with breakfast and dinner) for 1 week, and azithromycin (tablets, Libbs, São Paulo), 500 mg once a day (2 hours after lunch) for the first 3 days (LAAz regimen); or 2) lansoprazole (capsules, Medley, São Paulo), 30 mg before breakfast, plus oxytetracycline (capsules, Bristol-Myers Squibb, São Paulo), 500 mg *q.i.d.,* plus furazolidone (tablets, UCI-Farma, São Paulo), 200 mg *t.i.d.* for 1 week (LTF regimen). Patients with active ulcers were also treated with ranitidine, 300 mg at bedtime for a total of 1 month.

Subjects were asked to record any adverse events occurring during the treatment period and to return for clinical check-up at the completion of the study therapy. Compliance and side-effects were assessed by means of a returned-tablets count and by direct interviews based on the "standard side-effect scoring system in studies exploring *H. pylori* treatment regimens", as proposed by de BOER et al.[10]. At this point, patients were also instructed to report to their study physician if they happened to use any other medication considered active against *H. pylori*, such as PPI, bismuth salts, or other antimicrobial agents, until follow-up examination.

Three months after the conclusion of the study therapy, subjects returned for reevaluation *H. pylori* eradication was assessed by endoscopy as at entry. Additionally, all patients underwent a ^{14}C-urea breath test (^{14}C-UBT). The breath test was performed following the instructions of product manufacturer. The ^{14}C-UBT was performed after a fasting period of 6 hours. The patient swolled a 1 micro Currie capsula of ^{14}C-UBT with 200 mL of water. After 10 minutes, a breath sample was collected. The samples were analysed with a liquid scintillation counter (Tri-Med Specialties Inc. USA). The results were considered positive when DPM >100[26].

Eradication was defined as negative result from all three tests (^{14}C-UBT, RUT and histology).

Statistical analysis

Demographic characteristics, *H. pylori* cure rates and side effects were compared using two-tailed Pearson χ^2 and Fischer's exact tests. All patients were evaluated in an intention-to-treat (ITT) analysis, in which patients without final *H. pylori* determination or with protocol violations were considered treatment failures. The per-protocol (PP) analysis included all subjects who took at least 80% of each study medication as prescribed and who completed the final *H. pylori* status assessment. Statistical significance was set at $P<0.05$.

RESULTS

One hundred and four patients entered the study. At entry, there were no significant differences between the two groups with regard to age, gender, smoking habits and endoscopic diagnoses (Table 1). Patient compliance, measured by returned-pill count, was considered good for both treatment regimens, with all but three patients taking more than 80% of their prescribed drugs (Table 2).

Both therapies were well tolerated by the most of the patients (Table 2). Although 23 (44.2%) in the LAAz group and 31 (59.6%) in the LTF group had experienced any degree of side effect, only 2 (3.8%) and 4 (7.6%), respectively in groups LAAz (diarrhea) and LTF (nausea), reported interference with their normal activities. Nevertheless, none of the side effects were considered clinically serious, and all but one patient completed the course.

All 104 patients were included in an ITT analysis. In the PP analysis, three patients were excluded from each group: one subject (1.9%) from the LTF group had withdrawn from the study due to treatment side effects (nausea); one patient from each group had taken less than 80% of the medication as directed, in spite of having completed the treatment; the other three patients excluded had failed to return for follow-up investigation.

Eradication results are shown in Table 3. The overall eradication rate in the LTF group was significantly better than in the LAAz group in both the ITT and PP analysis ($P<0.0001$). One patient in the LTF group took furazolidone, 200 mg *b.i.d*. instead of *t.i.d*., but *H. pylori* was eradicated nonetheless. Another patient in the LAAz group took amoxicillin, 1 g in the morning plus

TABLE 3 - Overview of treatment results

	LAAz	LTF	Significance (P)
Number of patients	52	52	P=1.0000
Patients lost at follow-up [n (%)]	2 (3.8%)	2 (3.8%)	NS
H. pylori eradication			
Per-protocol [n (%)]	14/49 (28.5%)	45/49 (91.8%)	P<0.0001
95% CI	(17.2-42.3%)	(81.4-99.3%)	
Intention-to-treat [n (%)]	14/52 (26.9%)	46/52 (88.4%)	P<0.0001
95% CI	(16.2-40.1%)	(77.5-95.1%)	
Smokers [n (%)]	3/15 (20.0%)	19/20 (95.0%)	P<0.0001
Non smokers [n (%)]	11/35 (31.0%)	27/30 (90.0%)	P<0.0001
Frequency of side effects			
Overall [n (%)]	23 (44.2%)	31(59.6%)	NS
Major [n (%)]	2 (3.8%)	4 (7.6%)	NS
Therapy discontinuation [n (%)]	0	1* (1.9%)	NS

* Nausea
CI: Confidence Interval

500 mg at night, instead of 1 g *b.i.d.*; in this case, eradication was unsuccessful.

There was good agreement between RUT, UBT and histology results. The three tests were positive for 38 patients and negative for 60 patients. Histology alone and UBT alone were positive for one patient each.

DISCUSSION

Choice of the ideal therapeutic scheme for *H. pylori* should be based on treatment effectiveness, safety, tolerability, interaction potential, and medication costs[12].

Azithromycin is a macrolide with excellent in vitro anti-*H. pylori* activity. It also exhibits a particularly attractive pharmacological profile in that, hypothetically, it could also curtail treatment duration, thus improving compliance and reducing costs[25] .

Clinical trials with azithromycin have showed considerable variation with respect to the regimens used and the results obtained[1, 3, 8, 17, 18, 20, 29, 31]. Several trials have tested azithromycin 500 mg/d for 3 days administered in fasting patients, in combination with a PPI and amoxicillin. The cure rates reached, on an ITT analysis, ranged from 93% to 22% [7, 20]. However, when azithromycin was administrated at mealtimes, which reduced its absorption by up to 50%[15], the cure rates ranged from 28% to 85%[2, 6, 7, 11, 32].

In this study, while treatment compliance has been highly satisfactory, the efficacy of the LAAz scheme, administered in fasting patients, has been low, with 28.8% eradication rate in the ITT analysis. In southeastern of Brazil, COELHO et al.[8] reported similar results. This could be attributed to several factors. Recent data suggest that 10- to 14-day triple therapies could achieve higher eradication rates than 7-day schedules[5]. CHEY et al.[7] showed that higher dose (1 g/d) of the drug was significantly better at curing *H. pylori* infection. An other possibility, it is that association of azithromycin with amoxicillin elicits a lower synergistic action than that achievable with nitroimidazoles. Resistance of *H. pylori* to azithromycin is another potential factor influencing treatment outcomes.

In the second study group, a combination of lansoprazole, tetracycline, and furazolidone was tested. In this study, the LTF scheme proved effective, with eradication rates of 91.8% and 88.4%, respectively in the PP and ITT analyses. These results are in agreement with the majority of studies published within the last 5 years that focused on furazolidone in triple or quadruple therapies, considering the heterogeneity of the specific regimens employed[9, 19, 22].

A major problem with furazolidone is the high rate of severe adverse effects[14, 28]. Some studies try to identify simpler dosage schemes, thus granting higher treatment conformity and perhaps greater tolerability. MALEKZADEH et al.[21] evaluated omeprazole 20 mg, tetracycline 500 mg, and furazolidone 200 mg twice daily for 4 days and for 7 days, they found that the eradication rates were unacceptable for *H. pylori* infection. However, MANSOUR-GHANAEI et al.[22] showed that when the medication were taken for 2 weeks the eradication rate were highly satisfactory.

In this study, we used furazolidone 200 mg 3 times for 7 days. It seems that furazolidone 600 mg/day for short period of time (7 days) is as effective as 10-14 days at curing *H. pylori* infection and it should have better compliance than 14 days schemes. In our study, 96% of patients took more than 80% of the prescribed medication, and only one patient interrupted the treatment plan. This may be explained by the fact that more time is spent with patients entering research protocols. The patients were better informed of the importance of *H. pylori* eradication and many of them chose to tolerate the adverse effects and to finish treatment. Therefore, the inconveniences of this association do not compromise its validity. Future studies may identify simpler dosage schemes, thus yelding greater tolerability.

CONCLUSION

The results clearly demonstrated that the LAAz regimen for *H. pylori* eradication was ineffectual for the studied population. However, the LTF scheme, although less practical, is effective and may represent an economically viable alternative for *H. pylori* eradication in developing countries.

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RESUMO - ***Racional*** - Ainda não está estabelecida a melhor terapêutica anti-*H. pylori*. ***Objetivo*** - Avaliar a erradicação de *H.pylori* usando tetraciclina e furazolidona versus amoxicilina e azitromicina em terapia tríplice com lansoprazol no nordeste do Brasil. ***Pacientes e métodos*** - Cento e quatro pacientes infectados por *H. pylori*, diagnosticado através do teste rápido da urease e histologia, foram selecionados aleatoriamente para receber: lansoprazol (30 mg *q.d.),* tetraciclina (500 mg *q.i.d.),* furazolidona (200 mg *t.i.d.)* por 7 dias (LTF; n = 52); ou lansoprazol (30 mg *b.i.d.)* e amoxicilina (1 g *b.i.d.)* por 1 semana, mais azitromicina (500 mg *q.d.)* nos primeiros 3 dias (LAAz; n = 52). A erradicação de *H.pylori* foi avaliada 3 meses após término da terapia através do teste da urease, histologia e teste respiratório usando uréia marcada com ^{14}Carbono. ***Resultado*** - A erradicação do *H. pylori* foi atingida em 46 de 52 (88.4%, 95% CI: 77.5%-95.1%) pacientes no grupo LTF e em 14 de 52 (26.9%, 95% CI: 16.2%-40,1%) pacientes no grupo LAAz. Na análise per-protocolo, a taxa de erradicação foi de 91.8% (95% CI: 81.4%-97.3%) e 28.5% (95% CI: 17.2%-42.3%), respectivamente no grupo de LTF e LAAz. ***Conclusão*** - O esquema com LAAz ofereceu taxas de erradicação inaceitáveis. Por outro lado, o esquema com LTF representa alternativa adequada para erradicação de *H.pylori*.

DESCRITORES – *Helicobacter pylori.* Infecções por *Helicobacter*, quimioterapia. Tetraciclina. Furazolidona. Amoxicilina. Azitromicina. Bombas de próton, antagonistas & inibidores.

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