LOW EFFICACY OF AN ULTRA-SHORT TERM, ONCE-DAILY DOSE TRIPLE THERAPY WITH OMEPRAZOLE, AZITHROMYCIN, AND SECNIDAZOLE FOR *HELICOBACTER PYLORI* ERADICATION IN PEPTIC ULCER

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RHCFAP/3062

SILVA FM et al. - Low efficacy of an ultra-short term, once-daily dose triple therapy with Omeprazole, Azithromycin, and Secnidazole for *Helicobacter pylori* eradication in peptic ulcer. **Rev. Hosp. Clín. Fac. Med. S. Paulo 57**(1):9-14, 2002.

PURPOSE: To determine the eradication rate of an ultra-short treatment schedule for *Helicobacter pylori* infection in a population with peptic ulcers, using omeprazole, secnidazole, and azithromycin in a once-daily dose for 3 days.

METHODS: Thirty patients with peptic ulcer diagnosed by upper endoscopy and for *Helicobacter pylori* infection by rapid urease test and histologic examination received omeprazole 40 mg, secnidazole 1000 mg, and azithromycin 500 mg, administered once daily for 3 days. A follow-up exam was performed 12 weeks after the end of the treatment. Patients who were negative for *Helicobacter pylori* infection by rapid urease test and histologic examination were considered cured.

RESULTS: Patients were predominantly female, and the mean age was 50 years. Duodenal peptic ulcer was found in 73% of the patients. Eradication was achieved in 9 of the 28 (32%) patients as determined from the follow-up endoscopic exam. The eradication rate by intention to treat was 30%. Side effects were present in 3% of the patients, and compliance to treatment was total.

CONCLUSIONS: In spite of the low rate of side effects and good compliance, the eradication index was low. A possible drawback of this therapy is that it reduces the efficacy of macrolide and nitroimidazole compounds in subsequent treatments.

DESCRIPTORS: **Peptic Ulcer/Treatment. *Helicobacter pylori*/Eradication. Secnidazole/Therapeutic use. Azithromycin/Therapeutic use. Omeprazole/Therapeutic use.**

When the presence of *Helicobacter pylori* is associated with peptic ulcer disease, eradication of this bacterium leads to the cure of the disease[1], despite the fact that an optimal antibiotic schedule for its eradication has not yet been found[2]. The complexity and adverse effects of treatment and bacterial resistance to the medications provide different eradication rates, with several treatment regimens used to date[3-5]. As a general rule concerning bacteria that are sensitive to antibiotics, a longer period of treatment and different types of medication promote a higher eradication rate for the chosen regimen[6]. However, this longer treatment regimen may also bring more side effects and result in lower compliance[7].

Currently, therapy with 2 antibiotics plus a proton pump inhibitor, one of them clarithromycin and the other a nitroimidazole compound, have resulted in high eradication rates in several countries[8-12]. Concerning our patients, the treatment with the proton pump inhibitor, clarithromycin, and tinidazole eradicated *H. pylori* infection in 75% of those patients previously untreated[13]. Many studies report good eradication rates using a short-term treatment[14-18]. The possibility of using a regimen including macrolide and nitroimidazole compounds, which have prolonged plasma half-lives[19-21], seemed to promise a short-term treatment with a high efficacy. Therefore, the main objective of this study was to assess the eradication rate of *H. pylori* achieved through the combined use of omeprazole,

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azithromycin, and secnidazole with a once-daily dose for 3 consecutive days in a cohort with peptic ulcer.

PATIENTS AND METHODS

Thirty consecutive outpatients who underwent upper digestive endoscopy were invited to participate in the study.

To be included in the study, patients had to have scar or active peptic ulcer in the stomach or duodenum and also had to be infected by *H. pylori.*

Patients were excluded from the study if they: 1) were previously treated for *H. pylori* infection, 2) had a previous antibiotic treatment (within the last 3 months), 3) were younger than 16 years of age, 4) were pregnant or lactating mothers, or 5) had previous gastric surgery or severe illness.

The Ethics and Science Committee of our institution approved the study, and all patients signed the written informed consent statement.

The diagnose of the infection:

H. pylori infection was diagnosed with the rapid urease test (RUT) and from histologic examination (H & E stain) of 2 gastric biopsy specimens (antrum and body). The criteria for determination of *H. pylori* eradication were a negative RUT and negative histology as determined from biopsy specimens obtained during upper digestive endoscopy performed 12 weeks after the end of treatment.

The treatment:

The schedule of treatment consisted of azithromycin 500 mg, secnidazole 1000 mg, and omeprazole 40 mg, given once daily for 3 consecutive days. At the end of treatment, the remaining pills were counted, side effects were checked, and patients were requested to discontinue the anti-ulcer medication, except for the symptomatic use of antacids.

Statistical analysis was performed using a SPSS v.8.0 (SPSS Inc., USA) software package.

RESULTS

The baseline characteristics of the population studied are shown on table 1. The predominant sex was female (63%), and the percentage of duodenal ulcer was nearly 7 times higher than gastric ulcers. The mean age, close to the median age, was 50 years. Tobacco and non-steroidal anti-inflammatory drug (NSAID) users, as well as alcoholic patients, comprised a small number of the patients. Migrants were more numerous than the natives of the city of São Paulo.

Treatment compliance was fully successful (all patients took all doses of the medication adequately), and only 1 patient complained of a side effect (a light skin rash). Two patients declined the follow-up endoscopic exam. They were excluded from the per protocol determination of the *H. pylori* eradication rate. The *H. pylori* eradication rate was 30% for all patients included in the study (intention–to-treat rate) and 32% for the patients who underwent endoscopic examination (per-protocol rate) (Table 2).

Table 1 - Clinical data.

Patients (n)		30
Age (years)	Mean	51
	Median	50
	Range	27 - 77
Women		63%*(19/30)*
Migrants		60%*(18/30)*
Blacks		10%*(3/30)*
Duodenal ulcer		87%*(26/30)*
Tobacco users		20%*(6/30)*
NSAIDs users		17%*(5/30)*
Alcohol users		10%*(3/30)*

DISCUSSION

H. pylori eradication rates were very low in our series, even considering that ours is a developing country and that most patients were female (who tend to harbor strains resistant to secnidazole)[22]. A higher *H .pylori* eradication rate was expected. It is well known that the prevalence of resistant bacteria varies from place to place in the same country[22,23], but in our center, the prevalence of resistant bacteria was not known. The rates of eradication obtained were lower than the ones obtained in a previous study carried out with our patients with the use of clarithromycin, tinidazole, and a proton pump inhibitor given twice a day for 7 days[13], where a 75% eradication rate was achieved for those patients who were previously untreated. Several studies performed in Brazilian centers with a triple-agent treatment regimen of a week or less have also proved effective[24-27].

Azithromycin is said to be a compound similar to clarithromycin for the eradication of *H. pylori*[28,29]. Unfortunately this antibiotic is not always applicable, since it has a lower reliability than clarithromycin for a 3-day

Table 2 - *Helicobacter pylori* eradication rates.

	n / **%**	Confidence Interval (95%)
Per protocol (n = 28)	9 / **32%**	13% - 50%
Intention to treat (n = 30)	9 / **30%**	12% - 47%

treatment, alone or in combination with other drugs [30-33]. Secnidazole is a nitroimidazole derivative and does not differ from metronidazole. However, it has a prolonged plasma half-life, and for this reason, secnidazole is the first-choice treatment for many diseases[19].

For those patients from a disadvantaged cultural and social background, as in our series, shorter and simpler schedules result in better eradication rates. Shorter, simpler treatment regimens lead to higher compliance, lower cost, and fewer side effects, which are important issues for good outcomes[34,35]. From this standpoint, the therapy used in this study was close to the optimal treatment. All patients took their medication properly, and only one reported side effects.

The use of 2 antibiotics with an even longer plasma half-life in a daily dose, plus the ultra short-term use of omeprazole (only 3 days), can jeopardize the efficacy of the regimen.

In fact, the number of intakes and *in loco* action of the antibiotics might play an important role on *H. pylori* eradication, since it is possible that the ultra-short regimen reduces antibiotic concentration on the gastric mucosa[36]. Omeprazole induces bacterial growth, and short-term use can prevent an opportunity for a more powerful antibacterial action[37].

Increasing the number of days of the regimen would make the treatment similar to the regimen that uses the proton pump inhibitor, tinidazole, and clarithromycin twice a day for 7 days, which would result in abandoning the main attractive features of the regimen reported here, that is, its simplicity, shorter schedule, lower cost, and reduced side effects.

Nevertheless, the use of this treatment regimen might reduce the efficacy of macrolides and nitroimidazoles in later treatments for those patients in whom we were unable to eradicate *H. pylori* infection[38,39].

RESUMO RHCFAP/3062

SILVA FM e col. – Baixa eficácia de um tratamento tríplice de curta duração, em dose única diária, para erradicação do *Helicobacter pylori* em pacientes ulcerosos com Omeprazol, Azitromicina e Secnidazol. **Rev. Hosp. Clín. Fac. Med. S. Paulo 57**(1):9-14, 2002.

OBJETIVO: Testar a eficácia de um esquema ultra-curto de erradicação do *H. pylori* em uma população de ulcerosos, usando Omeprazol, Secnidazol e Azitromicina em dose única diária por três dias.

PACIENTES E MÉTODOS: Trinta doentes portadores de úlcera péptica, documentada por exame endoscópico e com infecção pelo *H. pylori* confirmada pelo teste da urease e exame histológico, foram tratados com Omeprazol 40mg, Secnidazol 1000 mg e Azitromicina 500mg dados em dose única diária por três dias. Em controle endoscópico realizado 12 se-

manas após o término do tratamento, foram considerados curados da infecção os pacientes que apresentaram o teste da urease e exame histológico negativos para a bactéria.

RESULTADOS: As mulheres predominaram (63%), a idade média foi de 50 anos e a úlcera duodenal foi identificada em 73% dos pacientes. Nos 28 doentes que realizaram o exame de controle, a erradicação foi constatada em nove (32%). Por intenção de tratamento o índice foi de 30%. A adesão ao tratamento foi total e houve um baixo índice de efeitos adversos (3%).

CONCLUSÃO: O esquema apesar de proporcionar alta adesão e poucos efeitos adversos, apresenta baixa taxa de erradicação, mesmo em se considerando um país em desenvolvimento e apresenta como possível agravante comprometer a eficácia de outros macrolídeos e nitroimidazólicos no uso de esquemas de erradicação subseqüentes.

DESCRITORES: **Úlcera péptica/terapia. *Helicobacter pylori*/terapia. Secnidazol/uso terapêutico. Azitromicina/uso terapêutico. Omeprazol/uso terapêutico.**

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Received for publication on March 19, 2001.