Available online at www.sciencedirect.com
SCIENCE DIRECT
Digestive and Liver Disease 37 (2005) 826–831
Digestive and Liver Disease
www.elsevier.com/locate/dld

Alimentary Tract

β-Lactamase inhibition with clavulanic acid supplementing standard amoxycillin-based triple therapy does not increase *Helicobacter pylori* eradication rate

P. Crispino [a], F. Iacopini [a], R. Pica [a], A. Consolazio [a], A. Bella [c], C. Cassieri [a], F. Nardi [b], P. Paoluzi [a,*]

[a] *Gastroenterology Unit, Department of Clinical Sciences, Policlinico Umberto I, Viale del Policlinico 157, 00161 Rome, Italy*
[b] *Department of Pathology, University "La Sapienza", Rome, Italy*
[c] *Statistical Division, Institute of Health, Rome, Italy*

Received 5 May 2005; accepted 20 July 2005
Available online 15 September 2005

Abstract

Background. Antibiotic resistance is the main reason of failure for *H. pylori* eradication and β-lactamases produced by resistant *H. pylori* strains is a possible mechanism underlying ineffectiveness of an amoxycillin-based triple therapy.

Aim. To investigate the benefit of using clavulanic acid associated with amoxycillin compared with amoxycillin alone in a standard triple therapy.

Methods. A total 172 *H. pylori*-positive dyspeptic patients were randomised to a daily treatment with esomeprazole (20 mg bid), clarithromycin (500 mg bid) and either amoxycillin plus clavulanic acid (1 g bid) or amoxycillin (1 g bid) alone for 1 week. *H. pylori* status was defined by histology and urea breath test at entry and following 8 weeks from the end of therapy by urea breath test and antigen faecal assessment.

Results. At intention-to-treat and per-protocol analysis eradication rates achieved by amoxycillin plus clavulanic acid (72 and 78%) were higher, but not significantly, than those achieved by amoxycillin alone triple therapy (62 and 72%). Compliance was good, side-effects mild and with a similar incidence in both regimens.

Conclusions. Clavulanic acid supplemented to amoxycillin-based standard triple therapy does not significantly increase the *H. pylori* eradication rate with standard triple therapy.

Keywords: Amoxycillin; Antibiotic resistance; Clavulanic acid; *Helicobacter pylori*

1. Introduction

Helicobacter pylori is the main aetiological factor of chronic gastritis and peptic ulcer disease (PUD), and its eradication seems to reduce the risk of low-grade MALT lymphoma and gastric adenocarcinoma [1]. According to 2001 Maastricht consensus conference, a standard treatment for *H. pylori* infection is based on the combination of a proton pump inhibitor (PPI) associated with two antibiotics, such as amoxycillin, clarithromycin or nitroimidazole [2]. Although these regimens have been reported to induce *H. pylori* eradication in >80% of patients [1,2], several factors influence efficacy of therapy and above all bacterial resistance to antibiotics. While resistance to metronidazole and clarithromycin has been well demonstrated, data regarding amoxycillin are scanty and often inconsistent, the frequency being very low in some geographic areas [3–6] and high in others [7,8]. Taking into account several evidences [3,7–9], indicating that the production of β-lactamases by *H. pylori* is an important mechanism underlying the resistance to amoxycillin, it could be hypothesised that clavulanic acid may increase

* Corresponding author. Tel.: +39 06 4903 35; fax: +39 06 4903 35.
E-mail address: paolo.paoluzi@uniroma1.it (P. Paoluzi).

1590-8658/$30 © 2005 Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l.
doi:10.1016/j.dld.2005.07.010

the *H. pylori* eradication rates through the inactivation of β-lactamases and also taking a direct part in the bactericide action. Aim of the present study was to compare the efficacy and tolerability of two amoxycillin-based triple therapies, one associated with clavulanic acid and another not, in the eradication of *H. pylori* infection in dyspeptic patients.

2. Methods

2.1. Study population

Presence of *H. pylori* infection was established by histological evaluation of two biopsies collected from the antrum and corpus (haematoxylin–eosin and modified Giemsa staining) and ^{13}C-urea breath test (UBT). A total of 172 consecutive dyspeptic patients, *H. pylori*-positive to both tests, were enrolled in the study. Exclusion criteria were previous attempts of *H. pylori* eradication, intake of bismuth, antisecretory drugs (H_2-antagonists or PPIs) or antibiotics within the last 3 months prior to the study entry; a past history of intolerance and/or allergy to study drugs; gastric cancer; pregnancy and lactating. The study was performed in accordance with the principles of the 1983 Declaration of Helsinki and the local ethic committee approved the study protocol. All patients gave written informed consent for inclusion in the study.

At entry, all patients were stratified according to the presence of PUD, gastro-oesophageal reflux disease (GORD) and non-ulcer dyspepsia (NUD). GORD was diagnosed according to the presence of heartburn and/or endoscopic diagnosis of reflux oesophagitis; in cases of coexistence of PUD and GORD, patients were included in the PUD group.

2.2. Study design and sample size

The investigation was designed as a randomised, single-blind open-label study. Hypothesising a minimal difference of 15% between the eradication rates achieved in the two groups, with an α error <5% and a power of 90%, the number of patients to be enrolled in each group was calculated to be 86.

2.3. Study regimens

Patients were randomised to receive one of the following two regimens for 1 week: esomeprazole 20 mg bid, clarithromycin 500 mg bid, and either amoxycillin (875 mg) plus clavulanic acid (125 mg) 1 g bid (ECAC), or amoxycillin 1 g bid (ECA). All study drugs were administered in the form of commercial packages.

2.4. Assessment of H. pylori eradication

H. pylori status was evaluated after 8 weeks following the end of the treatment by using *H. pylori* antigen faecal assessment and ^{13}C urea breath test (UBT Test, Cortex Italia, Milan, Italy) and was considered as to be negative (achievement of eradication) when both tests gave negative results.

2.5. Tolerability and compliance

A clinical examination was performed within 1 week after the end of therapy to evaluate the occurrence of side-effects and compliance. Upon assignment of therapy, each patient was informed concerning the possibility of clinical side-effects related to the study drugs, but was encouraged to continue if not serious. A side-effect was defined as severe when daily activity was impossible and required withdrawal from the therapy or reduction of dosage; as moderate when normal daily activity was limited but did not require a modification of dosage schedule; as mild when it did not interfere with normal daily activity and consumption of drugs was continued unmodified. Tolerability was evaluated by the assessment of type and severity of predefined symptoms. Recovery from side-effects after reduction or discontinuation of the study drug or need for specific therapy were also recorded. Compliance was assessed by a predefined chart and was judged as good if the patient had taken >90% of the total number of tablets.

2.6. Statistical analysis

Analysis of data was performed according to intention-to-treat (ITT) and per-protocol (PP) criteria. All randomised patients were included in the ITT analysis. Patients lost to follow-up and with low compliance were considered as drop-outs and excluded from the PP analysis. Demographic differences between study groups were compared using chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. A multiple logistic regression model was used to determine the relationship between the outcome, eradication success, and a set of explanatory variables, as well as to test the significance of each variable while simultaneously accounting for demographic and risk factors. The following variables were included in the model: age ($\leq$50 and >50), sex, smoking habit (yes/no), alcohol intake (yes/no) and type of disease (PUD, NUD and GORD).

A p-value <0.05 was considered to be statistically significant. Data analyses were performed by BMDP (Biomedical Computer Programs, Berkley, University of California Press, Los Angeles, CA, USA).

3. Results

3.1. Characteristics of study population

Of the 172 *H. pylori*-positive patients enrolled in the study, 89 were randomised to receive ECA and 83 ECAC treatment. Demographic and clinical characteristics of the study