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Beta-lactamase inhibitor enhances *Helicobacter pylori* eradication rate

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Abstract. Ojetti V, Migneco A, Zocco MA, Nista EC, Gasbarrini G, Gasbarrini A (Gemelli Teaching Hospital, Catholic University of Rome, Rome, Italy). Beta-lactamase inhibitor enhances *Helicobacter pylori* eradication rate. *J Intern Med* 2004; **255:** 125–129.

Objectives. One-week triple therapy, a combination of acid suppression with two antibiotics, is the gold standard for anti-*Helicobacter pylori* treatment. There is increasing evidence of *H. pylori* resistance to classical triple therapy. Recently, it was reported that the amoxicillin–clavulanate combination had a slightly higher activity than amoxicillin alone against *H. pylori*, and that β-lactamase inhibitors had '*in-vitro*' antibacterial activity against *H. pylori*.
Setting. To evaluate the efficacy of 1 week triple therapy omeprazole, clarithromycin and amoxicillin plus clavulanate compared with omeprazole, clarithromycin and amoxicillin for *H. pylori* eradication. The study was open randomized.
Subjects. Sixty dyspeptic patients (36 male, 24 female; mean age 53 ± 9 years) with *Helicobacter pylori* infection never treated before, were enrolled and randomly assigned to two different 7-day triple therapies: (i) ($n = 30$) amoxicillin 875 mg plus clavulanic acid 125 mg b.i.d., clarithromycin 500 mg b.i.d., omeprazole 20 mg b.i.d. (ACCO); (ii) ($n = 30$) amoxicillin 1 g b.i.d., clarithromycin 500 mg b.i.d., omeprazole 20 mg b.i.d. (ACO). Bacterial eradication was assessed by ^{13}C-urea breath test 4–6 weeks after therapy. Information on gastrointestinal symptoms and antibiotic-related side-effects were recorded using a questionnaire.
Results. All patients completed the study. A significantly higher *H. pylori* eradication rate with ACCO compared with ACO: (26/30) 86.6 vs. (20/30) 66.6%, respectively ($P < 0.05$) were observed. No major side-effects were reported, whilst 8% patients complained of mild side-effects; no significant differences were noted between the two groups.
Conclusions. Our results suggest that amoxicillin and clavulanate in combination achieve a higher *H. pylori* eradication rate than amoxicillin alone, without any increase in side-effects. The combination of amoxicillin and clavulanate may represent an alternative therapeutic scheme for the treatment of *H. pylori* infection.

Keywords: amoxicillin–clavulanate, β-lactamase inhibitor, higher *H. pylori* eradication rate, omeprazole, side effects, triple therapy.

Introduction

Helicobacter pylori, a microaerophilic, Gram-negative bacterium that colonizes the mucous layer of the gastric epithelium is the causative agent of type B gastritis, peptic ulcer, gastric cancer [1, 2] and extradigestive diseases [3, 4]. At least a third of the world's population is infected by *H. pylori* [5]. Many drug schemes have been proposed to reach complete eradication [6, 7]. One of the most common schemes is the 'standard triple therapy', resulting from the combination of a proton pump inhibitor (PPI) [8] or ranitidine bismuth citrate (RBC) with two antibiotics (clarithromycin and amoxicillin or a nitroimidazole), administered for 1 week [9]. This therapy has been reported to achieve an eradication rate ranging from 85 to 90% [10, 11]. Many agents have been proposed as second-line therapies in case of treatment failure [12] or impossibility to use the standard first-line therapies (i.e. history of adverse reactions to one of the drugs to be administered). Further trials to evaluate the effectiveness of these alternative therapies should be performed. Many factors may someway affect the results of the above-mentioned

first-line therapy, such as antibiotic drug resistance, low patient compliance and therapy-related side-effects [13]. Actually, one of the common causes of therapy failure is poor compliance due to the great number of tablets to be taken per day and/or the side-effects that may occur [14]. The development of antibiotic resistant strains is the major cause of eradication failure [15, 16, 17], and culture with antimicrobial susceptibility testing has been proposed as a method to reach a higher eradication rate [7]. It is, however, an expensive, time-consuming and not always available procedure.

Nowadays treatment failure is a significant problem in clinical practice, and the possibility to use simpler eradication schemes or new drugs should be regarded as the most promising way to improve the efficacy of the eradication therapy.

The oral antibacterial combination of the semi-synthetic antibiotic amoxicillin and the β-lactamase inhibitor clavulanate potassium is indicated in bacterial infections caused by susceptible β-lactamase-producing strains, such as *Haemophilus influenzae, Moraxella (Branhamella), Staphilococcus aureus, Escherichia coli, Klebsiella* spp. and *Enterobacter* spp. [18].

Some recent studies proposed this antibacterial combination in the treatment of *H. pylori* infection.

Horii *et al.* analysed the *in vitro* antibacterial activity of β-lactamase inhibitors in two studies [19]. The first study evaluated the activity of various β-lactamase inhibitors, including clavulanate, sulbactam and tazobactam, against *H. pylori*. The results suggested a high *in vitro* antibacterial activity of these agents against *H. pylori*. The combination of amoxicillin with clavulanate increased the antibacterial activity even more [19]. The second study confirmed the previous data, and showed that clavulanate and sulbactam alone were able to decrease the viable counts of *H. pylori*, depending on the antibiotic concentrations [20].

Dore *et al.* also investigated the *in vitro* activity of a penicillin and β-lactamase inhibitor combination against *H. pylori*, and showed that moderately resistant strains to amoxicillin had a high *in vitro* sensitivity to the combination amoxicillin–clavulanic acid [21].

Finally, Vcev *et al.* showed that the triple therapy scheme with omeprazole, metronidazole and amoxicillin plus clavulanic acid achieved '*in vivo*' an higher eradication rate compared to the triple therapy with omeprazole, metronidazole and amoxicillin alone [22].

Aim of our study was to evaluate the efficacy of the 1 week triple therapy omeprazole, clarithromycin and amoxicillin plus clavulanate in comparison with the 1 week 'classical' triple therapy omeprazole, clarithromycin and amoxicillin for *H. pylori* eradication.

Materials and methods

From March 2002 to June 2002, 60 dyspeptic *H. pylori* positive patients (36 males, 24 females, mean age 53 ± 9 years), referring to the Gastrointestinal Department and to the Endoscopy Service of the 'A. Gemelli' teaching Hospital of Rome, were consecutively enrolled. All patients were informed of the aims of the study and agreed to participate.

The study was approved by the ethical committee of our university.

The study was open randomized. *Helicobacter pylori* infection was determined by ^{13}C-urea breath test [23]. Patients who had been using antibiotics during the 6 months before the study were excluded. Exclusion criteria were also a history of hypersensitivity to the studied drugs, concomitant serious diseases, pregnancy, use of bismuth compound, PPI or H_2-receptor antagonists, and previous *H. pylori* eradication therapy.

Only patients who fulfil Maastricht criteria for *H. pylori* eradication [24] were included in our study. Patients were randomized into two different groups: the first study group received treatment with amoxicillin 875 mg plus clavulanate 125 mg (twice daily), clarithromycin 500 mg (twice daily), omeprazole 20 mg (twice daily) (ACCO) for 7 days, and the second group received treatment with amoxicillin 1 g (twice daily), clarithromycin 500 mg (twice daily), omeprazole 20 mg (twice daily) (ACO) for 7 days. Eradication was defined as the absence of *H. pylori* infection, assessed with ^{13}C-urea breath test, 4–6 weeks after completing the antimicrobial therapy. Both per-protocol and intention-to-treat analysis were performed. Patients were adequately informed and motivated to therapy, and thoroughly followed up. Moreover, patients were asked to grade the most common side-effects that occurred during therapy. In particular, each subject received a self-administered questionnaire, slightly modified from de Boer *et al.* [25], to record the development of symptoms such as nausea, vomiting, abdominal

pain, taste disturbances, diarrhoea, constipation and skin rash, from nil to severe. Severity scores were assigned as follows: nil (score 0, no side-effects), mild (score 1, could be disregarded), moderate (score 2, bad enough to call a physician, but treatment could be continued and was tolerated), severe (score 3, interfering with activity at work, requiring discontinuation of the therapy). At enrolment and at the end of therapy, each patient completed the validated dyspepsia questionnaire of Buckley *et al.* [26], to obtain information on gastrointestinal (GI) symptoms (pyrosis, epigastric pain, belching, bloating, halitosis and nausea).

Statistical analysis

The two groups were compared using a Student *t*-test for unpaired data. The level of significance was set at a 5% probability level. Results are expressed as mean ± standard error.

Results

All patients completed the study.

A significantly higher eradication rate was obtained with 'ACCO' scheme, with an eradication rate of 86.6% (26 of 30 patients), when compared with the 'ACO' scheme, with an eradication rate of 66.6% (20 of 30 patients). This difference was statistically significant ($P < 0.05$).

The per-protocol and intention-to-treat analyses showed to be the same in our study, because of the absence of drop out events.

The overall patients' compliance to both eradication schemes was good, with all patients completing the prescribed therapy. Both treatments were very well tolerated, no major side-effects being reported.

Only few (five of 60 patients = 8.3%) patients did complain of mild therapy-related side-effects, without any significant differences between the two groups. In particular, two patients in the 'ACCO' group (group 1) complained of mild side-effects (one taste disturbance and one nausea), whilst one patient in the 'ACO' group complained of a score 2 diarrhoea, and two patients in the 'ACO' group complained of a score 1 taste disturbance.

H. pylori-eradicated patients showed a significant reduction of the intensity of all gastrointestinal symptoms evaluated, except for nausea and halitosis (Tables 1 and 2).

Table 1 Prevalence of gastrointestinal symptoms in dyspeptic patients submitted to ACCO therapy at enrolment (T0) and 6 weeks after eradication (T1)

Symptoms	T0 (%)	T1 (%)	*P*
Pyrosis	43.3	23	<0.05
Epigastric pain	46.6	27	<0.05
Belching	40	23	<0.05
Bloating	36.6	27	<0.05
Halitosis	46.6	38.5	NS
Nausea	33.3	30	NS

NS, not significant.

Table 2 Prevalence of gastrointestinal symptoms in dyspeptic patients submitted to ACO therapy at enrolment (T0) and 6 weeks after eradication (T1)

Symptoms	T0 (%)	T1 (%)	*P*
Pyrosis	43.3	30	<0.05
Epigastric pain	46.6	30	<0.05
Belching	50	35	<0.05
Bloating	33.3	25	<0.05
Halitosis	46.6	40	NS
Nausea	26.6	30	NS

NS, not significant.

Conversely, in the treated but not eradicated patients the prevalence of gastrointestinal symptoms did not change significantly.

Discussion

The increasing knowledge on the impact of *H. pylori* infection on human disease results in several treatment guidelines [27, 28]. Nowadays, advisable first-line treatments are those recommended by the Maastricht 2001 Consensus Conference Guidelines: a PPI or RBC twice daily plus clarithromycin and amoxicillin, or plus clarithromycin and metronidazole [24]. The ideal treatment, with an eradication rate approaching 100% and low incidence of side-effects, has not yet been identified. Treatment success is related to different factors: patients' compliance, bacterial resistance to antibiotics, treatment duration and antibiotic related side-effects [12, 13]. The selection of an adequate eradication therapy should consider side-effects, cost-effectiveness and antimicrobial sensitivity.

Furthermore, the optimal duration of eradication treatment remains controversial. Data available from literature show that 1-week treatment is

sufficient to achieve results that are not improved by a second treatment week [29].

It is widely accepted that the main factor that affects the outcome of a standard treatment for *H. pylori* eradication is the development of antibiotic resistant strains [11, 15]. Infact, in our geographical area, we are assisting to a progressive decrease in eradication rate with conventional therapy. Another important feature is the access of antimicrobial drugs to the microenvironment where *H. pylori* grows and the pharmacological properties of these drugs that sometimes are not yet completely understood.

Several studies have evaluated new drugs, such as rifabutin [30], fluoroquinolones, levofloxacin [31], moxifloxacin [32] and the association of clavulanate and amoxicillin [22] in the eradication of *H. pylori*.

Most *H. pylori* strains are susceptible to amoxicillin, an important component of many combination therapies for *H. pylori* eradication. The isolation and initial characterization of the first-reported stable amoxicillin-resistant clinical *H. pylori* strain (the Hardenberg strain) has been published previously, but the underlying resistance mechanism was not described [33]. Recent study showed that amoxicillin has a bactericidal effect on *H. pylori*, but has less-inhibitory effects in the stationary growth phase and against cell-adherent or slowly growing *H. pylori* [19].

The β-lactamase inhibitors such as clavulanate decreased *in vitro* the viable counts of *H. pylori*. The exposure to these β-lactamase inhibitors resulted in morphological changes of cell shape, cell-wall disintegration and cell lysis [20]. Clavulanate was the most active of these β-lactamase inhibitors, causing a decrease in viable counts and morphological changes such as short filamentous to spheroplast formation and lysis [20].

These preliminary observation indicate that the amoxicillin and clavulanate may be a promising alternative in anti-*H. pylori* schemes.

As regards the side-effects occurring during administration of this association, data from literature show that only 4.4% of patients discontinue therapy because of drug-related side-effects. The most commonly reported side-effects with probable or suspected relationship to amoxicillin plus clavulanate are diarrhoea (2.9%) and vomiting (2.2%) [34].

In the present study we show that the association of clarithromycin, omeprazole and amoxicillin plus clavulanate achieves a higher eradication rate when compared with clarithromycin, omeprazole and amoxicillin alone.

The amoxicillin plus clavulanate-based scheme may improve efficacy of *H. pylori* eradication with no increase in side-effects compared with amoxicillin alone.

The low prevalence of side-effects reported with our triple therapy (amoxicillin plus clavulanate) confirmed the data from literature.

In conclusion the combination of amoxicillin and clavulanate is well tolerated and may represent an alternative treatment for *H. pylori* infection.

Conflict of interest statement

No conflict of interest was declared.

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