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Comparison of Omeprazole, Metronidazole and Clarithromycin with Omeprazole/Amoxicillin Dual-Therapy for the Cure of *Helicobacter pylori* Infection

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Abstract

In this randomized, multicenter trial, we evaluated the effectiveness and side effect profile of a modified omeprazole-based triple therapy to cure *Helicobacter pylori* infection. The control group consisted of patients treated with standard dual therapy comprising omeprazole and amoxicillin. One hundred and fifty-seven *H. pylori* infected patients with duodenal ulcers were randomly assigned to receive either a combination of omeprazole 10 mg, clarithromycin 250 mg and metronidazole 400 mg (OCM) given three times daily for 10 days (n = 81), or a combination of omeprazole 20 mg and amoxicillin 1 g (OA) given twice daily for 14 days (n = 76). Prior to treatment and after 2 and 6 weeks, gastric biopsies from the antrum and corpus were obtained for histology and *H. pylori* culture. *H. pylori* infection was cured in 97.4% after OCM and in 65.8% after OA in the per-protocol analysis ($p < 0.001$) (intention-to-treat analysis: 93.4% and 63.2%, respectively). *H. pylori* was successfully cultured in 122 patients (77%). The overall rate of metronidazole resistance was 19.7% (24/122), no primary resistance to clarithromycin or amoxicillin was found. In the OCM group, all patients infected with metronidazole-sensitive *H. pylori* strains (n = 51) and those infected with strains of unknown susceptibility to metronidazole (n = 14) were cured (100%), while 77% (10/13) of those harboring metronidazole-resistant strains were cured of the infection ($p = 0.36$). Side effects leading to premature termination of treatment occurred in 2.5% of the patients in the OCM group and in 1.4% of the OA group. We conclude that combined treatment with omeprazole, clarithromycin and a higher dose of metronidazole is highly effective in curing *H. pylori* infection, and that this regimen remains very effective in the presence of metronidazole-resistant strains.

Key Words

Helicobacter pylori omeprazole
Clarithromycin
Metronidazole
Amoxicillin
Antimicrobial resistance

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Introduction

It is well recognized that *Helicobacter pylori* is the principal cause of chronic gastritis and duodenal ulcer disease [1]. In 1994, the National Institute of Health Consensus Development Conferences on *H. pylori* in peptic ulcer disease recommended antimicrobial therapy for ulcer patients whether on the first presentation of illness or on recurrence [2]. However, in routine practice, cure of the infection has proven to be difficult. Complex regimens such as the combination of bismuth salts, metronidazole and tetracycline although highly effective are limited by poor patient compliance or antimicrobial resistance to nitroimidazoles [3]. Dual therapy comprising omeprazole and amoxicillin (OA) is simple, well tolerated, and cures *H. pylori* infection in up to 90% depending on the daily dose of omeprazole [4, 5], however, variable cure rates have been reported [6–8]. Omeprazole-based triple-therapy regimens consistently cure *H. pylori* infection in 90% and more [9–12], however, few data exist about the efficacy of such a regimen in the presence of metronidazole-resistant *H. pylori* strains. In this randomized study, we evaluated the effectiveness and tolerability of combined treatment with omeprazole, clarithromycin and metronidazole (OCM) each given three times daily in comparison with standard dual therapy comprising omeprazole 20 mg b.i.d. and amoxicillin 1 g b.i.d. In addition, pre- and post-treatment resistance to the antibiotics in use was determined.

Methods

Study Population

Patients aged 18–80 years with *H. pylori*-associated duodenal ulcers were included in this randomized, multicenter study. Exclusion criteria were an additional gastric or pyloric ulcer, use of bismuth compounds or antibiotics 4 weeks prior to endoscopy, regular consumption of steroids, NSAIDs or more than 100 mg of acetylsalicylic acid per day, previous ulcer surgery, pregnancy, renal insufficiency, known allergy to those antibiotics used and contraindications of biopsy.

Therapy

Patients were randomly treated with either a combination of omeprazole 10 mg, clarithromycin 250 mg and metronidazole 400 mg (OCM) given three times daily with meals for 10 days, or standard dual therapy comprising omeprazole 20 mg and amoxicillin 1 g (OA) given twice daily with meals for 14 days. The latter regimen was the only approved anti-*H. pylori* therapy in 1993 when the present study was planned. Drug compliance was assessed by pill count and a diary where patients recorded adverse events.

Endoscopy and Histology

Endoscopic examinations were conducted prior to treatment, after 2 weeks to document ulcer healing and after 6 weeks to determine cure of *H. pylori* infection. At each endoscopy, 4 biopsy specimens from the antrum and 2 from the corpus were obtained for histologic examination, a number considered to ensure reliable detection of *H. pylori* [13]. Biopsy specimens were placed in neutral buffered formalin. HE staining was performed to grade gastritis, and Warthin-Starry staining to detect and grade mucosal *H. pylori* colonization according to the Sydney System [14]. Patients who were *H. pylori*-negative at histology and culture prior to treatment were withdrawn and treated conventionally.

H. pylori *Culture and Susceptibility Testing*

Two antral biopsy specimens were taken for microbiological examinations. Culture biopsies were transported to the Department of Microbiology, in Portagerm pylori transport medium (BioMérieux, Marcy-l'Etoile, France) within 24 h. Immediately after arrival, *H. pylori* was cultured on Pylori agar (BioMérieux) and Wilkins-Chalgren agar medium supplemented with 10% horse blood and Skirrow Antibiotic Supplement (Oxoid, Basingstoke, UK). *H. pylori* was identified by typical gram stain morphology, and by biochemical tests positive for oxidase, catalase and urease. For susceptibility testing, cells were harvested from a 2- to 3-day fresh culture on Wilkins-Chalgren agar and transferred to 1 ml of brucella broth (Difco, Augsburg, Germany). Inoculum density was adjusted to McFarland 3–4 which represents approximately 0.5×10^9 colony-forming units (CFU)/ml. Motility and morphology were checked by phase contrast microscopy. The suspension was discarded if more than one fourth of rounded organisms or clumped aggregates were detected. A Wilkins-Chalgren agar plate was flooded and allowed to dry for 5–10 min. One E-test strip (AB Biodisk, Solna, Sweden) was placed on the agar, and the plate was incubated under microaerophilic conditions (11% O_2, 9% CO_2, 80% N_2) for 2–3 days until sufficient growth was visible. The results were read according to the manufacturer's instructions. Interpretation criteria for clarithromycin were sensitive for MIC values ≤ 0.125 mg/l and resistant for ≥ 2 mg/l. The corresponding values for metronidazole were 8 and 32 mg/l, and for amoxicillin 2 and 4 mg/l, respectively.

Definition of H. pylori *Status*

At baseline examination, patients were considered *H. pylori*-infected when either histology or culture was positive. Cure of *H. pylori* infection was assessed at least 4 weeks after completion of treatment, and was defined as being *H. pylori*-negative on histology and culture.

Statistical calculations were performed using the statistical software package SPSS/PC+5.0 (SPSS Inc., USA). Rate comparisons were made with the χ^2 test. The study was approved by the Ethics Committee of the University of Munich.

Results

One-hundred fifty-seven DU patients infected with *H. pylori* were randomized to one of the two treatment groups, 81 to the OCM group, and 76 to the OA group. The overall study population consisted of 101 men and 56

Table 1. Characteristics of study patients

	OCM	OA	p
Mean age, years	47.8 ± 15.1	50.7 ± 14.8	0.53
Male/female	56/25	45/31	0.19
Consumption of			
Alcohol	58	48	0.37
Coffee	59	54	0.45
Smoking	43	38	0.57

Table 2. Ulcer healing and *H. pylori* cure rates following treatment with OCM in patients infected with metronidazole-sensitive or metronidazole-resistant *H. pylori* strains and following treatment with OA

	OCM	OA
Ulcer healing	overall 81/81 (100)	74/76 (97.3)
H. pylori cure		
Per protocol	76/78 (97.4)	48/73 (65.8)
Intention-to-treat	76/81 (93.4)	48/76 (63.2)
MET-sensitive	51/51 (100)	
MET-resistant	10/13 (77)	
Unknown susceptibility	14/14 (100)	

Figures in parentheses are percentages. MET = Metronidazole.

women (age range 26–78 years, mean age 49.6 years). There was no statistically significant difference in the patient characteristics between the OCM and the OA group (table 1). One patient of the OCM group (1.2%) was lost to follow-up. Side effects leading to premature termination of treatment occurred in 2 of 81 patients (2.5%) in the OCM group (diarrhea), and in 1 of 74 patients (1.4%) in the OA group ($p > 0.5$) (allergic skin reaction). In all cases, the side effects were self-limiting after termination of treatment. These 4 patients were therefore excluded from the per-protocol analysis. Minor adverse events were observed in 13 patients (16.7%) and in 9 patients (11.8%) in the respective treatment groups ($p > 0.5$), mainly mild diarrhea, taste disturbance, mild nausea, headache.

Ulcer healing determined 2 weeks after initiation of treatment was achieved in 81/81 patients in the OCM group, and in 74/76 (97.3%) of the patients in the OA group. The 2 patients without documented ulcer healing were also excluded from the per-protocol analysis. Cure of *H. pylori* infection was documented in 97.4% of patients (76/78) following treatment with OCM (intention-to-treat analysis 93.4%; 76/81) and in 65.8% of patients (48/73) after OA therapy (intention-to-treat analysis 63.2%; 48/76) ($p < 0.001$). In 122 of 157 patients, culture for *H. pylori* was successful (77%). Twenty-four of the available 122 pretreatment *H. pylori* isolates (19.7%) were resistant to metronidazole (13/64 in the OCM group, and 11/58 in the OA group). In the OCM group, all patients infected with metronidazole-sensitive *H. pylori* strains (n = 51) and those infected with strains of unknown susceptibility to metronidazole (n = 14) were cured (100%), while 77% (10/13) of those harboring metronidazole-resistant strains were cured of the infection ($p = 0.36$). In the OA group, 8 of 11 (73%) patients infected with metronidazole-resistant strains were cured of the infection. None of the pre- and posttreatment isolates were resistant to clarithromycin or amoxicillin (table 2).

Discussion

Although *H. pylori* is sensitive to a number of antimicrobials and anti-ulcer agents in vitro, curing the infection in vivo has proven to be a difficult task. Multi-drug regimens are generally required to achieve consistent high cure rates. In 1993, Bazzoli et al. [9] introduced a simple and highly effective treatment strategy combining omeprazole with two antibiotics given for 1 week. Subsequent trials using different combinations of antimicrobials were able to confirm those data [10–12]. In the present study, we demonstrated a high efficacy of more than 95% in curing *H. pylori* infection with a modified omeprazole-based triple therapy comprising clarithromycin and metronidazole given three times instead of twice daily for 10 days. This finding is in agreement with recently reported studies using standard-dose triple-therapy regimens [15, 16].

A well-recognized problem of various anti-*H. pylori* therapy regimens is primary resistance of *H. pylori* against metronidazole ranging from 11 to 25% in Western countries [17–19], and even up to 95% in developing countries [20]. While resistance of *H. pylori* against metronidazole has been shown to be a fundamental problem for the original standard triple therapy comprising bismuth, tetracycline and metronidazole [3], the effectiveness of the new omeprazole-based triple-therapy regimens in curing infection with metronidazole-resistant *H. pylori* isolates has not been investigated thoroughly. In the present study, the overall frequency of metronidazole resistance was close to 20%. However, in the 13 patients of the OCM group who

harbored metronidazole-resistant *H. pylori* isolates, 10 (77%) were cured of the infection suggesting that even in the presence of metronidazole resistance this regimen is still effective, either due to the higher daily dose of metronidazole (3 × 400 mg) or to the extended length of treatment. More strikingly, all other patients in the OCM group (100%) who were infected with metronidazole-sensitive strains or strains with unknown susceptibility were cured, underlining the excellent efficacy of this regimen.

Clarithromycin is one of the most active compounds ($MIC_{90} > 0.03$ g/ml) among the various antimicrobials and anti-ulcer agents that have been tested in vitro against *H. pylori* [21, 22]. When used as monotherapy, clarithromycin has the ability to cure *H. pylori* infection in up to 54% of patients [23]. Today, clarithromycin is an essential compound of triple-therapy regimens comprising omeprazole and metronidazole or amoxicillin [24]. Reported resistance rates of *H. pylori* against clarithromycin range from 0 to 12% [15, 24–26]. In our study, primary or acquired resistance of *H. pylori* against clarithromycin did not occur, again indicating the high suitability of this antimicrobial for anti-*H. pylori* combination regimens.

Dual therapy with OA has initially shown promising results in curing *H. pylori* infection, in particular when higher daily doses of omeprazole have been used [4, 5, 27]. However, other investigators failed to reproduce these data [6–8], and subsequent studies revealed that this regimen may be sensitive to various, mostly patient-related factors. It has been shown that lack of compliance, short duration of therapy, smoking and pretreatment with omeprazole are independent factors with a negative influence on treatment success, while older age of patients, high-grade gastritis and gastric ulcer are predictors for a higher success rate [28]. In this study, the control group was treated with the standard dosage of omeprazole, 20 mg b.i.d. and amoxicillin 1 g b.i.d., since this regimen was the only approved therapy for treatment of *H. pylori*-associated ulcers in 1993 when the present study was planned. We observed a 66% cure rate of *H. pylori* infection, which is basically in agreement with our own previous data [27] and a recent meta-analysis by van der Hulst et al. [29]. Based on 53 treatment arms, including a total of 2,275 patients using omeprazole given twice daily in combination with amoxicillin for 2 weeks, they found a mean eradication rate of 62%. These findings certainly do not justify the use of this regimen as a first-line treatment, however, dual therapy regimens comprising high-dose omeprazole (e.g., 120 mg/day) might be useful in the future when antimicrobial resistance of *H. pylori* may become a considerable problem.

Another important finding in this study was the excellent rate of ulcer healing determined 2 weeks after initiation of therapy in both treatment arms (OCM 100%, OA 97.3%). These findings are basically in agreement with a recently published randomized double-blind study by Labenz et al. [30] showing that continuation of antisecretory drug therapy beyond anti-*H. pylori* therapy may be unnecessary to achieve rapid symptom relief and reliable healing of uncomplicated duodenal ulcers. In conclusion, combined treatment with OMC for the cure of *H. pylori* infection in duodenal ulcer patients is significantly more effective than standard dual therapy with OA. Even in the presence of metronidazole-resistant *H. pylori* isolates is this modified omeprazole-based triple-therapy regimen very effective, most likely due to the higher daily dose of metronidazole.

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