The combination of omeprazole, amoxycillin, and clarithromycin eradicates *Helicobacter pylori* in 95% of patients—7 days of therapy is as good as 10 days

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More than half of the known *Helicobacter pylori* strains are resistant to metronidazole, according to previous Hong Kong studies. The response rates to treatment regimens that comprise metronidazole as one of the antimicrobial agents have usually been disappointing in cases involving metronidazole-resistant strains. The objective of this open cohort evaluation was to assess the efficacy of an alternative regimen that combines omeprazole with amoxycillin and clarithromycin in *Helicobacter pylori*–positive ulcer and non-ulcer patients in Hong Kong. Furthermore, we aimed to investigate if 7 days were as good as 10 days of therapy. We studied 186 *Helicobacter pylori*–positive subjects; 149 subjects received 7 days of combination therapy and 37 subjects received 10 days. Our results showed that the overall *Helicobacter pylori* eradication efficiency was identical (94.6%) for both treatments. The incidences of adverse effects were very similar (16.8% versus 16.2%) and both treatments were well tolerated. Thus, we propose that omeprazole in combination with amoxycillin and clarithromycin should be considered as one of the first-line therapies for patients with *Helicobacter pylori* infection in Hong Kong.

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Key words: Amoxicillin; Antibiotics, combined/therapeutic use; Clarithromycin; Helicobacter infections/therapy; Helicobacter pylori; Omeprazole

Introduction

The eradication of *Helicobacter pylori* is the main objective in the treatment of peptic ulcers that are associated with this organism.[1] Success in the elimination of *H. pylori* results not only in the healing of ulcers but also in the prevention of ulcer relapse.[2,3] The ulcer re-bleeding rate has also been shown to decrease significantly when *H. pylori* has been successfully eradicated.[4,5] Recent preliminary evidence suggests that patients with *H. pylori*–positive non-ulcer dyspepsia also benefit from anti–*H. pylori* therapy.[6]

According to a recent review,[7] previous reports on a variety of anti–*H. pylori* regimens have yielded different results; eradication efficiency ranges from 55% to 96%. There is, however, still no consensus treatment regimen that can be adopted as the ideal first-line anti–*H. pylori* therapy. One of the important factors that influences the eradication efficiency is the sensitivity of *H. pylori* to metronidazole.[8-10] Previous reports[7-10] indicate that metronidazole-resistant *H. pylori* strains generally do not respond well to anti–*H. pylori* combination therapy that contains metronidazole. We have previously reported that the eradication efficiency can be as low as 50% in metronidazole-resistant cases, and as high as 93% in metronidazole-susceptible strains when using combination therapy that contains metronidazole.[11] In Hong Kong, the overall frequency of metronidazole-resistant cases of *H. pylori* has been shown to be over 50%,[11] which would explain the poor results when metronidazole is used in conjunction with omeprazole and either amoxycillin or clarithromycin.

The combination of omeprazole, amoxycillin, and clarithromycin, when given over 1 to 2 weeks, gives a very encouraging overall eradication efficiency of

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Table 1. Frequencies of *H. pylori* eradication

	OAC7* frequency (%)	OAC10† frequency (%)	P value
Duodenal ulcer	65/69 (94.2)	9/9 (100)	ns
Gastric ulcer	14/15 (93.3)	2/2 (100)	ns
Non-ulcer dyspepsia	62/65 (95.4)	24/26 (92.3)	ns
Overall	141/149 (94.6)	35/37 (94.6)	ns

*OAC7 patients received twice daily treatment with omeprazole 20 mg, amoxycillin 1 g, clarithromycin 500 mg for 7 days
†OAC10 patients received OAC7 treatment for 10 days
ns not significant

88.0% (range, 85.5% to 90.5%).[7] We have performed an open prospective study using these agents to evaluate whether they can be adopted as first-line combination therapy for patients in Hong Kong. We have also evaluated how 7 days compares with 10 days of treatment.

Materials and methods

Subjects

One hundred and eighty-six *H. pylori*–positive patients were randomised to receive one of the anti–*H. pylori* therapies described below. All patients underwent diagnostic gastroscopy for dyspepsia, and were shown to have *H. pylori* infection by a rapid urease test, as described previously.[12] Of the 186 subjects, 149 (71 men [mean age, 47 years]; 78 women, [mean age, 41 years]) received omeprazole 20 mg, amoxycillin 1 g and clarithromycin 500 mg twice daily for 7 days (hereafter referred to as the 'OAC7' group). The other 37 subjects (20 men [mean age, 45 years]; 17 women [mean age, 44 years]) were given the same combination therapy for 10 days (the 'OAC10' group). A recruitment of a 4:1 (OAC7:OAC10) ratio was predetermined simply because we thought that 7 days' therapy should be just as good as, and more economical than, 10 days' treatment.

Patients with a duodenal ulcer (n=69 for OAC7; n=9 for OAC10) or gastric ulcer (n=15 for OAC7; n=2 for OAC10) were given omeprazole 20 mg/day for a further 3 weeks after the combination therapy to expedite ulcer healing. Repeat endoscopy and rapid urease test were performed 1 week later (4 weeks after completion of the combination therapy) in these subjects. Subjects who refused to have repeat endoscopy, and those with non-ulcer dyspepsia (n=65 for OAC7; n= 26 for OAC10) were evaluated clinically when they returned for the ^{13}C-urea breath test 4 weeks after completion of the combination therapy. Drug compliance and adverse drug effects were assessed at the end of the triple therapy in all cases.

^{13}C-urea breath test

The ^{13}C-urea breath test was performed according to Klein et al[13] except for the modification of using a lower dose of ^{13}C-urea (100 mg instead of 125 mg). A difference between the 30 minutes and the base-line breath samples of >5 delta units/mL was considered as a positive result.

Statistics

Student's *t* test, Fisher's exact test, and the Chi squared test with or without Yates correction were used to compare the results of the OAC7 and OAC10 treatment groups. Differences were considered not significant if the P value were >0.05.

Results

H. pylori *eradication*

Compliance in this group of patients was 100%. The overall *H. pylori* eradication efficiency was identical (94.6%) in the two treatment groups (Table 1). There were also no significant differences between the two treatments for each of the subgroups (duodenal ulcer, gastric ulcer, non-ulcer dyspepsia). All subjects who returned for repeat endoscopy (35 patients with duodenal ulcer; 13 patients with gastric ulcer) were found to have healed ulcers. The other ulcer subjects who refused to have repeat endoscopy had all become asymptomatic when they were reassessed prior to the ^{13}C-urea breath test.

Drug compliance and adverse effects

Each patient included in this study completed their treatment course despite adverse effects. Adverse effects were very similar between the two groups: 16.8% for OAC7 and 16.2% for OAC10 (Table 2). The majority of patients with adverse effects complained of disturbed taste sensation and/or loose stool. Only a small percentage described nausea or worsened epigastric discomfort. The worst adverse effect observed was oropharyngeal and oesophageal candidiasis in one of the OAC7 patients. This patient experienced odynophagia and progressive dysphagia. Fortunately, the symptoms and candidiasis resolved after a course of oral nystatin.

Table 2. Incidence of adverse effects

	OAC7, n=149 No. (%)	OAC10, n=37 No. (%)
Disturbed taste	22 (14.8)	4 (10.8)
Loose stool/diarrhoea	15 (10.1)	4 (10.8)
Worsened dyspepsia	3 (2.0)	1 (2.7)
Minor skin rash	1 (0.7)	0
Candidiasis	1 (0.7)	0
Overall side effect incidence	25 (16.8)	6 (16.2)

Discussion

The ideal anti-*H. pylori* treatment should have an eradication efficiency of >90%; a very low side effect profile so that a high compliance rate can be achieved; and a short course of therapy that not only improves the compliance but also reduces the cost. Currently, very few combination regimens can claim an overall mean eradication efficiency in excess of 90%. According to a recent review by van der Hulst et al,[7] the combination of omeprazole, bismuth, tetracycline, and metronidazole (quadruple therapy), given for 1 week, can achieve a mean eradication efficiency of 96.4% (range, 94.1% to 97.9%). This combination appears to be the most effective so far, in terms of eliminating *H. pylori* infection. The purpose-designed agent, Pylorid (ranitidine bismuth citrate), has also recently been claimed to have *H. pylori* eradication efficacy in >90% of patients where it was combined with clarithromycin.[14,15] Pylorid had to be given for 4 weeks, however, and the clarithromycin had to be given for 2 weeks. Furthermore, these are only preliminary data which will require further studies to confirm drug efficacy.

We have observed an equally effective *H. pylori* eradication efficiency (approximately 95%) in this study by combining omeprazole with amoxycillin and clarithromycin for 7 days. Our results compare well with those reported in a multi-centre study, with a similar sample size, by Lind et al.[16] They observed an eradication efficiency of 96% in 131 *H. pylori*–positive duodenal ulcer patients who had received the OAC7 treatment. In our study, we have confirmed that there is no added advantage by prolonging the treatment to 10 days.

We have deliberately avoided using metronidazole in the design of the combination therapy because our previous study[11] and studies by others[17] have reported an overall frequency of metronidazole resistance of >50% in Hong Kong. Our previous experience[11] of metronidazole-containing regimens has been highly unsatisfactory, although others[18,19] report very favourable results when metronidazole is combined with bismuth and tetracycline with or without omeprazole. The latter drug in combination with bismuth may have helped to overcome the metronidazole resistance by a mechanism that is poorly understood.[20,21] The OAC7 regimen was well tolerated in our patients and the side effect profile was very low. In terms of efficacy (>90%), side effects (<20%), and duration (7 days), OAC7 qualifies, in our opinion, as an ideal anti-*H. pylori* therapy; it should be considered as one of the first-line combination treatments for *H. pylori* infection in Hong Kong. We would propose using either the quadruple therapy or the combination of Pylorid and clarithromycin as a second line of therapy if OAC7 were to fail.

In conclusion, omeprazole in combination with amoxycillin and clarithromycin can eradicate *H. pylori* in the majority of cases (approximately 95%) in Hong Kong, where resistance of the organism against metronidazole is high. The drugs in the OAC7 scheme should also be considered as the first-line agents in *H. pylori*–positive cases in other regions in south-east Asia, where the metronidazole resistance rate is generally very similar to that in Hong Kong.

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