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Comparison of Cetraxate-based and Pantoprazole-based Triple Therapies in the Treatment of *Helicobacter pylori* Infection

Background. Recent studies suggest that cetraxate possesses anti-*Helicobacter pylori* (*H. pylori*) activity. We therefore conducted this pilot study to investigate the efficacy of a cetraxate-based triple therapy and to compare the regimen with proton pump inhibitor-based triple therapy.
Methods. From April 2001 to January 2002, a total of 58 *H. pylori*-infected patients were randomly assigned to 1 of 2 regimens for 1 week: cetraxate plus clarithromycin and amoxicillin (CCA group) or pantoprazole plus clarithromycin and amoxicillin (PCA group). Follow-up endoscopy was performed at 8 weeks after the end of treatment to assess the treatment response.
Results. Intention-to-treat analysis showed that the eradication rates of the CCA group (n = 27) and PCA group (n = 31) were 70.4% and 93.5%, respectively. The CCA group had a significantly lower eradication rate than the PCA group ($p = 0.03$). Per-protocol analysis also showed similar results (69.2% *vs.* 96.7%, $p = 0.01$). However, the frequency of adverse events in the CCA group was lower than that of the PCA group (3.7% *vs.* 25.8%, $p = 0.03$). Univariate analysis showed that the eradication rate was significantly related to proton pump inhibitor therapy (93.5% *vs.* 70.4%, $p = 0.03$) and smoking habit (66.7 % *vs.* 88.4%, $p = 0.05$), but multivariate analysis disclosed that proton pump inhibitor therapy was the only independent factor predicting treatment success ($p < 0.05$).
Conclusions. Cetraxate-based triple therapy is less effective than pantoprazole-based triple therapy in the treatment of *H. pylori* infection. However, the former has a lower frequency of adverse effects than the latter.

The discovery of *Helicobacter pylori* (*H. pylori*) heralded a breakthrough in the field of gastroenterology. The microorganism is linked to a spectrum of gastrointestinal diseases, including chronic gastritis, duodenal and gastric ulcer, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma (MALToma).[1-3] Cure of *H. pylori* infection prevents ulcer recurrence,[2] and decreases the recurrence of intestinal-type gastric cancer in patients who have undergone endoscopic resection of the primary tumor.[4] In addition, eradication of *H. pylori* results in complete regression of 60-83% of MALTomas.[5] Recently, we also disclosed that cure of *H. pylori* infection prevented ulcer formation in patients with ulcer-like functional dyspepsia.[6]

At present, the most popular first-line treatment for *H. pylori* infection are that recommended by the Maastricht 2-2000 Concensus Report[7]: a proton pump inhibitor (PPI) or ranitidine bismuth citrate twice daily, plus clarithromycin (500 mg twice daily) and amoxicillin (1 g twice daily), or plus clarithromycin (500 mg twice daily) and metronidazole (500 mg twice daily). Treatment has been shown to be effective and safe in numerous clinical trials but, as expected, when applied to the whole population, the rate of success is reduced.[8,9] In Taiwan, our study revealed that a failure rate of PPI-based triple therapy was 24%.[10] Therefore, it is still necessary to search for a universally well-tolerated, low cost and more effective anti-*H. pylori* regimen.

Cetraxate (a *p*-hydroxyphenyl-propionic ester of tranexamic acid drochloride) was introduced in 1976 as an anti-ulcer drug with a mucosal protective effect.[11-13] As reported,[13-15] it enhances ulcer healing by increasing mucus production, promoting synthesis of intramucosal prostaglandins, and improvement of mucosal blood flow, speeding up mucosal regeneration as well as inhibiting pepsinogen activation in gastric mucosa. Recently, Kimura *et al.*[16] demonstrated that cetraxate was able to inhibit the growth of *H. pylori*. Kamada *et al.*[17] also found that cetraxate increased the eradication rate of *H. pylori* in smokers. In addition, several other mucosal protective agents such as bismuth subcitrate and sucrafate have also been shown to enhance the anti-*H. pylori* activity of antimicrobials and have inhibitory effects on *H. pylori*.[18,19] We therefore designed this pilot study to investigate a cetraxate-based triple therapy in the treatment of *H. pylori* infection and prospectively compared the eradication efficacy of this new anti-*H. pylori* regimen with that of a PPI-based triple therapy. Additionally, we also examined the host factors influencing the outcomes of these eradication regimens.

METHODS

Patients

From April 2001 to January 2002, a total of 58 *H. pylori*-infected patients, at least 18 years of age, with endoscopically proven peptic ulcer diseases or gastritis were enrolled. The diagnosis of *H. pylori* infection was confirmed by rapid urease test and/or histological examination. Patients with more than 1 previous attempt to eradicate *H. pylori* were excluded. Other exclusion criteria was ingestion of non-steroidal anti-inflammatory drugs, antibiotics, bismuth, or proton pump inhibitors within the prior 4 weeks.

Study design

The eligible patients were randomized to either CCA (cetraxate 200 mg 4 times daily, clarithromycin 500 mg 2 times daily and amoxicillin 1 g 2 times daily) or PCA (pantoprazole 40 mg 2 times daily, clarithromycin 500 mg 2 times daily and amoxicillin 1 g 2 times daily) therapies. All drugs were administered for 7 days. Patients made a second visit for adverse events and compliance assessment at week 2. Repeated endoscopy with biopsy for rapid urease test and histological examination was performed at 8 weeks after the end of treatment. If patients refused follow-up endoscopy, urea breath tests were performed to assess *H. pylori* status. Eradication was defined as (1) negative results of both rapid urease test and histology or (2) a negative result of urea breath test. The study was approved by the Medical Committee of the Kaohsiung Veterans General Hospital.

Questionnaire

A complete medical history and demographic data were obtained from each patient, including age, sex, history of smoking, alcohol and coffee consumption. Smoking was defined as consumption of cigarettes 1 pack or more *per* week. Coffee or tea consumption was defined as drinking 1 cup or more *per* day.

Adverse events and drug compliance were prospectively evaluated. The adverse events were assessed according to a 3-point scale system. A score of 0 indicated no discomfort or minimal discomfort, 1 symbolized mild discomfort (annoying but not interfering with daily life), while 2 represented severe discomfort (interfering with daily life). Poor patient compliance was defined as taking less than 70% of the total medication.

Rapid urease test

The rapid urease test was performed according to our previous studies.[20,21] A biopsy specimen from the antrum

was placed immediately in 1 mL of a 10% solution of urea in deionized water (pH 6.8) to which 2 drops of 1% phenol red solution was added and incubated at 37 °C for up to 24 hours. If the yellowish color around the area of inserted specimen changed to bright pink within the 24-hour limit, the urease test was considered positive. In our laboratory, the sensitivity and specificity of the rapid urease test were 96% and 91%, respectively.[20]

Histological examination

The biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, and sectioned. One section, 4-μm thick, was cut and stained with hematolxylin and eosin to observe the presence of curved rod-shaped bacteria on the mucosal surface.[3,22] The specimens were interpreted by a histopathologist blinded to patient status and the results of other laboratory tests.

Urea breath test

The urea breath test was performed according to our previous studies.[23,24] The cutoff value was set at 4.8‰ of $\delta^{13}CO_2$. The staff who were blind to the *H. pylori* status performed the tests.

Statistical evaluation

The main measure of outcome was eradication of *H. pylori* infection. All patients were inclued in the intention-to-treat (ITT) analysis. Those patients who had poor compliance or violated protocol were excluded from *per*-protocol (PP) analysis. The differences of ages between the 2 groups were examined by Student's *t* test.

Differences in other patient characteristics and eradication rates between groups were analyzed by chi-square or Fisher exact tests. A multivariate analysis with logistic regression was applied to elucidate the host factors affecting the cure rate of *H. pylori* infection. Differences were considered significant at $p < 0.05$.

RESULTS

Patient population

Fifty-eight patients were randomized into the study. Among them, 2 (1 in each group) had poor compliance and were excluded from the PP analysis. The demographic data of the study population are shown in Table 1. There were no differences in the baseline characteristics of the 2 groups of patients.

Eradication of *H. pylori*

Table 2 showed the major outcomes of the study groups. ITT analysis showed that the CCA group had a

Table 2. The major outcomes of cetraxate-based and pantoprazole-based triple therapies

	Cetraxate group (n = 27)	PAC group (n = 31)	*p* value
Eradication rate			
Intention to treat	19/27 (70.4%)	29/31 (93.5%)	0.03[a]
Per-protocol	18/26 (69.2%)	29/30 (96.7%)	0.01[a]
Side effects	1/27 (3.7%)	8/31 (25.8%)	0.03[a]
Poor compliance	1/27 (3.7%)	1/31 (3.2%)	1.00

[a]Significant difference.

Table 1. Baseline characteristics of the study patients

	Cetraxate group (n = 27)	PCA group (n = 31)	*p* value
Age	51.9 ± 15.8	54.8 ± 11.9	0.43
Sex	8/19	7/24	0.56
Smoking	9/27 (33.3%)	6/31 (19.4%)	0.25
Daily alcohol use	0/27 (0.0%)	0/31 (0.0%)	-
Daily coffee use	1/27 (3.7%)	1/31 (3.2%)	1.00
Daily tea use	4/27 (14.8%)	3/31 (9.7%)	0.69
Endoscopic findings			0.11
GU	13/27 (48.1%)	9/31 (29.0%)	
DU	8/27 (29.6%)	15/31 (48.4%)	
GU + DU	6/27 (22.2%)	4/31 (12.9%)	
Gastritis	0/27 (0.0%)	3/31 (9.7%)	

GU = gastric ulcer; DU = duodenal ulcer.

significantly lower eradication rate than the PCA group (70.4% *vs.* 93.5%, *p* = 0.03). In the CCA group, 1 patient had poor compliance due to the development of severe skin rash. She took anti-*H. pylori* regimen for 3 days only, but successful eradication of *H. pylori* was achieved. In the PCA group, 1 patient suffered from drug allergy with severe skin rash after taking medication for 1 day. His *H. pylori* was not eradicated. PP analysis showed that the eradication rate of the CCA group was significantly lower than that of the PCA group (Table 2).

Adverse events

The frequency of adverse events in the CCA group was lower than that of the PCA group (3.7% *vs.* 25.8%, *p* = 0.03). Only 1 patient in the CCA group had an adverse event with skin rash. The adverse events in the PCA group included diarrhea (n = 1), nausea (n = 1), abdominal fullness (n = 1), dizziness (n = 2), skin rash (n = 1), abdominal pain (n = 1), insomnia (n = 1), abnormal taste (n = 2) and other (n = 2) (Tables 2 and 3). Only 2 patients (1 in each group) stopped the medication because of drug allergy with severe skin rash. The other patients had good drug compliance.

Factors influencing efficacy of eradication therapy

Table 4 shows the patient factors influencing the efficacy of eradication therapy. The eradication rates were significantly related to PPI therapy (93.5% *vs.* 70.4 %, *p* = 0.03) and smoking (66.7% *vs.* 88.4%, *p* = 0.05). The other factors (age, sex, alcohol drinking, coffee or tea consumption, presence of ulcer, side effects and drug compliance) did not significantly influence the efficacy of eradication therapy. Multivariate analysis with stepwise logistic regression disclosed that pantoprazole therapy was the only independent factor predictive of treatment success (*p* < 0.05). The odds ratio was 5.5, 95% confidence interval = 1.0 - 29.7 (Table 5).

DISCUSSION

Cetraxate is a potent cytoprotective agent effectively preventing the formation of gastric mucosal necrosis induced by HCl[25] and promoting ulcer healing.[11-13] Although the mechanism remains unclear, cetraxate inhib-

Table 3. The adverse events of cetraxate-based and pantoprazole-based triple therapies

		Cetraxate group (n = 27)	PAC group (n = 31)
Skin rash	Mild	0/27 (0.0%)	0/31(0.0%)
	Severe	1/27 (3.7%)	1/31 (3.2%)
Abdominal pain	Mild	0/27 (0.0%)	1/31 (3.2%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Constipation	Mild	0/27 (0.0%)	0/31 (0.0%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Diarrhea	Mild	0/27 (0.0%)	1/31 (3.2%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Dizziness	Mild	0/27 (0.0%)	2/31 (6.5%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Nausea	Mild	0/27 (0.0%)	1/31 (3.2%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Metallic taste	Mild	0/27 (0.0%)	0/31 (0.0%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Abdominal fullness	Mild	0/27 (0.0%)	1/31 (3.2%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Insomnia	Mild	0/27 (0.0%)	1/31 (3.2%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Abnormal taste	Mild	0/27 (0.0%)	2/31 (6.5%)
	Severe	0/27 (0.0%)	0/31 (0.0%)
Other	Mild	0/27 (0.0%)	2/31 (6.5%)
	Severe	0/27 (0.0%)	0/31 (0.0%)

Table 4. The host factors influencing the eradication efficacy of *H. pylori*

Principle parameter	Eradication rate (%)	*p* value
Age (y)		0.25
< 60	32/41 (78.0%)	
> 60	16/17 (94.1%)	
Sex		0.43
Female	14/15 (93.3%)	
Male	34/43 (79.1%)	
PPI therapy		0.03[a]
No	19/27 (70.4%)	
Yes	29/31 (93.5%)	
Smoking		0.05[a]
No	38/43 (88.4%)	
Yes	10/15 (66.7%)	
Alcohol		-
No	48/58 (82.8%)	
Yes	0/0 (0.0%)	
Coffee		0.32
No	47/56 (83.9%)	
Yes	1/2 (50.0%)	
Compliance		0.32
Good	47/56 (83.9%)	
Poor	1/2 (50.0%)	

[a]Significant difference.

Table 5. Stepwise logistic regression for host factors related to successful eradication of *H. pylori*

Risk factor	Coefficient	Standard error	OR (95% confidence interval)	*p* value
PPI therapy	1.696	0.859	5.5 (1.0-29.7)	0.048[a]
Smoking	-1.167	0.763	0.31 (0.1-1.4)	0.126

[a]Significant difference.

its the growth of *H, pylori* in vitro.[16] A recent study of Kamada *et al.*[17] also demonstrated that the *H. pylori* eradication rate in smokers was 55% in a PPI-based triple therapy with omeprazole plus amoxicillin and clarithromycin. Cetraxate combined with the aforementioned PPI-based triple regimen increased the eradication rate to 92%. These findings suggested that cetraxate possessed anti-*H. pylori* activity. Our work is the first study to investigate the efficacy of cetraxate-based triple therapies in the treatment of *H. pylori* infection. ITT analysis indicated that the average eradication rate of cetraxate-based triple therapies was 70.4%. According to the MACH2 study,[26] *H. pylori* eradication rate of pure antibiotic therapy with clarithromycin and amoxicillin was only 26%. The treatment response was lower than that of our cetraxate-based triple therapy. These results, taken together, suggest that cetraxate is able to increase the eradication rate of antibiotics in the treatment of *H. pylori*.

Currently, the mechanisms of anti-*H. pylori* activity of cetraxate are still unclear. It is, however, worth noting that cetraxate may enhance the nitric oxide of intramucosal prostaglandins, resulting in an increase in gastric mucosal blood flow.[27] It is therefore able to increase the delivery of antibiotics to the gastric mucosa by improving local circulation.[17] Further studies are warranted to elucidate the anti-*H. pylori* mechanisms of cetraxate.

Nonetheless, cetraxate-based triple therapy is less effective than PPI-based triple therapy. In the current study, pantoprazole plus clarithromycin and amoxicillin achieved an eradication rate of 93.5%. According to previous studies,[8,9,28] PPIs have 2 potential mechanisms in the treatment of *H. pylori*. One is the direct action on the bacteria,[28] and the other is the increase of intra-gastric pH value to stabilize the antibiotics and enhance the antibiotic sensitivity of *H. pylori*.[8,9]

So far, multiple factors have been reported to influence the treatment response of primary anti-*H. pylori* therapy. The main causes of failure include poor compliance of patients,[18] smoking,[29] antibiotic resistance,[30,31] excessive bac-terial burden,[32] coffee consumption,[33] short treatment duration,[29] doses of PPI and antibiotics.[3] In this study, univariate analysis showed use of PPI and smoking associated with treatment outcomes (*p* = 0.03 and 0.05, respectively). However, multivariate analysis in the current study showed that smoking was not an independent clinical factor influencing the eradication rates. In the past, a number of studies have also shown that smoking was associated with failure of *H. pylori* eradication.[29,34] Endoh *et al.*[35] demonstrated that smoking decreased gastric blood flow and mucus secretion, and thus might reduce the efficacy of treatment by decreasing the delivery of antibiotics to gastric mucosa. Because the number of cases in this study was relatively small, further studies are still needed to clarify the relationships between smoking and eradication outcomes and to elucidate whether *H. pylori*-infected patients should abstain from smoking while they receive eradication therapy.

In this study, only 1 patient in the CCA group suffered from skin rash. The adverse events in the PCA group included diarrhea, nausea, abdominal fullness, dizziness and skin rash, probably due to antibiotic therapy. The frequency of adverse events in the CCA group was lower than that of the PCA group (3.7% *vs.* 25.8%). Previous studies reveal that PPI may elevate intra-gastric pH to stabilize many antibiotics and increase plasma levels of clarithromycin.[8,9,36] This is one of the rationales to explain the higher frequency of adverse events and higher eradication rates of the PCA group.

In conclusion, our study is the first to investigate the efficacy of cetraxate-based triple therapy. This new regimen is less effective than pantoprazole-based triple therapy in eradicating *H. pylori*. However, the former has a lower frequency of adverse effects than the latter.

ACKNOWLEDGEMENTS

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