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The Therapeutic Effect of Proton Pump Inhibitors on *Helicobacter pylori*-positive Gastric Ulcers

M. SASAKII, T. JOH, Y. YOKOYAMA, K. SENO, K. TSUCHIDA, T. KUROKAWA AND M. ITOH

Department of Internal Medicine, Nagoya City University Medical School, Nagoya 467, Japan

Abstract

The aim of the present study was to elucidate the risk factors that could delay gastric ulcer healing when either a proton pump inhibitor or an H_2-receptor antagonist is used for gastric ulcer treatment.

Endoscopically-diagnosed gastric ulcer patients (216 men and 96 women, mean age: 57 ± 13 years) were investigated. All patients were consecutively recruited and randomly assigned to receive H_2-receptor antagonist ($n = 196$) or proton pump inhibitor ($n = 116$) treatment for eight weeks. Chi-squared tests and multivariate analysis to determine factors influencing ulcer healing were used to analyse the patients profiles, endoscopic findings, and *Helicobacter pylori*-infection status.

In the H_2-receptor antagonist group, the most important risk factor was a large ulcer size (> 2 cm diam.), followed by a linear shape of the ulcer, undermining tendency of ulcer, previous history of gastric ulcer, and *H. pylori* infection. In the proton pump inhibitor group, linear shape of the ulcer was the only significant risk factor for slow ulcer healing; other factors, including *H. pylori* infection, were insignificant.

These results indicate that ulcer morphology may be the most important information for predicting ulcer healing, and that *H. pylori* infection does not delay gastric ulcer healing when proton pump inhibitor treatment is used.

Previous reports (Doll et al 1958; Battaglia et al 1987) found smoking to be a strong risk factor in the slow healing of gastric ulcers, but others detected no effect (The Belgian Peptic Ulcer Study Group 1984; Okada et al 1984). Okada et al (1984) and Yokoyama et al (1992) reported that a patient's history of gastric ulcer or endoscopic findings, such as an undermining tendency to ulcer, size of ulcer, linear-shaped ulcer and angle ulcer location, are significant risk factors that could delay ulcer healing. In recent years, *Helicobacter pylori* has been recognized to play an important role in the pathogenesis of peptic ulcers. However, the effect of *H. pylori* infection on the healing of gastric ulcers is still controversial. Most reports (Bui et al 1991; O'Connor et al 1995; Ogoshi et al 1995; Kodama et al 1996; Penston 1996; Li et al 1997) suggest that *H. pylori* infection delays gastric ulcer healing, but others (Eberhardt & Kasper 1990; Tatsuta et al 1995) report no influence of infection on healing.

Correspondence: M. Sasaki, First Department of Internal Medicine, Nagoya City University Medical School, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467, Japan.

In this study, healing of *H. pylori*-positive and -negative gastric ulcers treated with either a proton pump inhibitor or an H_2-receptor antagonist were investigated to clarify the influence of *H. pylori* infection on ulcer healing.

Materials and Methods

Endoscopically-diagnosed gastric ulcer patients (216 men and 96 women, mean age: 57 ± 13 years) were enrolled in this study. Exclusion criteria were: intake of non-steroidal anti-inflammatory drugs (NSAIDs), severe concomitant diseases, low compliance, previous major gastrointestinal surgery and gastric cancer. All patients were consecutively recruited and randomly assigned to receive an H_2-receptor antagonist (ranitidine 150 mg, famotidine 20 mg, or nizatidine 150 mg twice daily) or a proton pump inhibitor (omeprazole 20 mg or lansoprazole 30 mg). After eight weeks, endoscopy was performed, and non-healed ulcers were considered to be slow healing. Several parameters were considered. The first parameter included the patient's sex, age of onset of gastric ulcer, complications, past history of gastric ulcer relapse, stress, smoking

and drinking. The second was endoscopic findings; number of ulcers (single or multiple); ulcer location (angulus or others); ulcer size (less or more than 20 mm); ulcer shape (round or irregular); linear shape; undermining tendency to ulcer; and bleeding. The third parameter was *H. pylori* infection status. Ulcer size was evaluated in every case using an open forceps as indicator. Histological examination (haematoxylin-eosin stain) and the rapid urease test were done using two biopsy specimens from the gastric antrum and two from the corpus to evaluate the status of *H. pylori* infection.

Statistical analysis

The Chi-squared test was used to evaluate the correlation between the parameters studied and healing. A multivariate analysis was used to reveal independent variables influencing ulcer healing. $P < 0{\cdot}05$ was considered significant.

Results

H. pylori infection was detected in 271 (86·9%) of 312 patients investigated. There were 312 patients enrolled in this study, but only 302 (210 men and 92 women, mean age 57 ± 13) completed the trial.

The patients who were most likely to have a slow-healing ulcer had a larger, linear-shaped ulcer, an undermining tendency to ulcer, an ulcer located in the angle, *H. pylori* infection, treatment with an H_2-receptor antagonist or previous history of gastric ulcer (Table 1). A multivariate analysis showed that treatment with an H_2-receptor antagonist was the most important factor in slowing ulcer healing. Linear-shaped ulcer, larger ulcer, an undermining tendency to ulcer, *H. pylori* infection, previous history of gastric ulcer, and locations of ulcer are also significantly important factors for predicting slow ulcer healing (Table 2).

One hundred and eighty-nine patients were treated with an H_2-receptor antagonist, and 113 patients were treated with a proton pump inhibitor. There were no significant differences in background factors between the two treatments (Table 3). In the H_2-receptor antagonist group, the patients who were most likely to have slow-healing ulcers had larger, linear-shaped ulcers, an undermining tendency to ulcer, *H. pylori* infection, previous

Table 1. Analysis of parameters considered for slow gastric ulcer healing.

		Healing rates at eight weeks		χ^2-test (P)
Background				
Sex	Males	80·0%	168/210	0·150
	Female	83·7%	77/92	
Age	< 65 years	79·5%	167/210	0·082
	> = 65 years	84·8%	(78/92)	
Smoker	Yes	81·1%	(154/190)	0·966
	No	81·3%	(91/112)	
Alcohol consumers	Yes	82·12%	(101/123)	0·716
	No	80·4%	(144/179)	
Complication	Yes	83·1%	(69/83)	0·583
	No	80·4%	(176/219)	
Stress	Yes	87·5%	(28/32)	0·330
	No	80·4%	(217/270)	
Previous history of ulcer	Yes	75·5%	(154/204)	0·003
	No	92·9%	(91/98)	
Endoscopic findings				
Number of ulcers	1	80·7%	(197/244)	0·724
	> = 2	82·83%	(48/58)	
Site	Angulus	70·5%	(79/112)	0·0003
	Others	86·3%	(164/190)	
Round shaped ulcer	Yes	83·3%	(145/174)	0·253
	No	78·1%	(100/128)	
Size	< 20 mm	86·4%	(216/250)	< 0·0001
	> = 20 mm	55·8%	(29/52)	
Bleeding	Yes	81·3%	(80/105)	0·101
	No	83·3%	(165/197)	
Linear shaped ulcer	Yes	51·4%	(19/37)	< 0·0001
	No	85·3%	(226/265)	
Undermining tendency to ulcer	Yes	50·0%	(20/40)	< 0·0001
	No	85·9%	(225/262)	
H. pylori infection	Yes	78·2%	(205/262)	0·001
	No	100%	(40/40)	
Treatment	Proton pump inhibitor	90·3%	(102/113)	0·002
	H_2-receptor antagonist	75·7%	(143/189)	

Table 2. Risk factors for delay in ulcer healing, according to multivariate analysis.

	Coefficient	Statistical significance for slow healing (P)
Treatment (H_2-receptor antagonist not proton pump inhibitor)	1·624	0·00000278
Linear shape	2·240	0·00036
Size (> =20 mm)	2·248	0·00037
Undermining tendency to ulcer	1·887	0·0031
H. pylori infection	1·472	0·0088
Previous history of ulcer	0·932	0·0220
Site (angulus)	0·894	0·0364
Smoking	0·031	0·0583
Stress	0·771	0·2081

history of gastric ulcer or an ulcer located in the angle (Table 4). However, in the proton pump inhibitor group, the patients most likely to have a slow-healing ulcer had an ulcer located in the angle, a linear-shaped ulcer, an undermining tendency to ulcer and larger ulcers (Table 4). In the H_2-receptor antagonist group, a multivariate analysis showed that the most important factor in slow healing of ulcers was having large ulcers (> 2 cm diam.). This was followed by linear-shaped ulcers, an undermining tendency to ulcers, previous history of gastric ulcer, and *H. pylori* infection (Table 5). In the proton pump inhibitor group, linear-shaped ulcer was the only significant factor. *H. pylori* infection had no significant effect.

Discussion

Many of the published reports on *H. pylori* infection and ulcer healing have concentrated on the effects of *H. pylori* eradication (Eberhardt & Kas-

Table 3. Comparison of background factors of H_2-receptor antagonist and proton pump inhibitor groups.

Background factor		H_2-receptor antagonist (n = 189)	Proton pump inhibitor (n = 113)	χ^2-test (P)
Sex	Males	133	77	0·684
	Females	56	36	
Age	< 65 years	137	73	0·150
	> =65 years	52	40	
Smoker	Yes	119	71	0·982
	No	70	42	
Alcohol consumers	Yes	69	54	0·055
	No	120	59	
Complication	Yes	50	33	0·605
	No	139	80	
Stress	Yes	19	13	0·692
	No	170	100	
Previous history of ulcer	Yes	127	77	0·865
	No	62	36	
Endoscopic findings				
Number of ulcers	1	156	88	0·319
	> =2	33	25	
Site	Angulus	67	45	0·447
	Others	122	68	
Round shaped ulcer	Yes	109	65	0·980
	No	80	48	
Size	< 20 mm	160	90	0·264
	> =20 mm	29	23	
Bleeding	Yes	60	45	0·154
	No	129	68	
Linear-shaped ulcer	Yes	22	15	0·675
	No	167	98	
Undermining tendency to ulcer	Yes	24	16	0·717
	No	165	97	
H. pylori infection	Yes	159	103	0·081
	No	30	10	

Table 4. Analysis of parameters considered for slow gastric ulcer healing in patients treated with H_2-receptor antagonists or proton pump inhibitor.

		H_2-receptor antagonist		Proton pump inhibitor	
		Healing rates	χ^2-test (P)	Healing rates	χ^2-test (P)
Background					
Sex	Males	75·9%	0·891	87·0%	0·088
	Females	75·0%		97·2%	
Age	< 65 years	75·2%	0·618	87·7%	0·209
	> = 65 years	76·9%		95·0%	
Smoker	Yes	77·3%	0·491	87·3%	0·170
	No	72·9%		95·2%	
Alcohol consumers	Yes	78·3%	0·528	87·0%	0·343
	No	74·2%		93·2%	
Complications	Yes	80·0%	0·405	87·9%	0·583
	No	74·1%		91·2%	
Stress	Yes	78·9%	0·725	100%	0·208
	No	75·3%		89·0%	
Previous history of ulcer	Yes	68·5%	0·001	87·0%	0·088
	No	90·3%		97·2%	
Endoscopic findings					
Number of ulcers	1	76·3%	0·666	88·6%	0·273
	> = 2	72·7%		96·0%	
Site	Angulus	65·7%	0·018	77·8%	0·0001
	Others	81·1%		100%	
Round shaped ulcer	Yes	78·0%	0·386	92·3%	0·394
	No	72·5%		87·5%	
Size	< 20 mm	82·5%	< 0·0001	93·3%	0·030*
	> = 20 mm	37·9%		78·3%	
Bleeding	Yes	68·3%	0·142	86·7%	0·294
	No	79·1%		92·6%	
Linear shaped ulcer	Yes	45·5%	0·0004	60·0%	0·0001
	No	79·6%		94·9%	
Undermining tendency	Yes	37·5%	< 0·0001	68·8%	0·002
	No	81·2%		93·8%	
H. pylori infection	Yes	71·2%	< 0·0001	89·3%	0·277
	No	100%		100%	

Table 5. Risk factors obtained by multivariate analysis for delay in ulcer healing for H_2-receptor antagonist or proton pump inhibitor treatment.

	H_2-receptor antagonist		Proton pump inhibitor	
	Coefficient	Statistical significance for slow healing (P)	Coefficient	Statistical significance for slow healing (P)
Size (> = 20 mm)	2·594	0·0007	1·617	0·389
Linear shape	2·140	0·006	4·606	0·001
Undermining tendency to ulcer	2·048	0·009	1·867	0·214
Previous history of ulcer	1·173	0·017	0·361	0·707
H. pylori infection	1·263	0·043	0·354	0·822
Smoking	0·034	0·070	0·029	0·450
Site (angulus)	0·784	0·135	1·884	0·054

per 1990; Bui et al 1991; O'Conner et al 1995; Ogoshi et al 1995; Sung et al 1995; Tatsuta et al 1995; Kodama et al 1996; Penston 1996; Li et al 1997). So far no consistent conclusion has been reached. In this study, we have assessed several factors, including *H. pylori* infection, which may influence the healing of gastric ulcers, using two statistical analysis methods, the Chi-squared test and multivariate analysis.

The results presented in Table 1 demonstrate that endoscopic findings, *H. pylori* infection and treatment are important for predicting ulcer healing

within eight weeks. Our results demonstrate that gastric ulcer healing was delayed by *H. pylori* infection. This is in agreement with Sung et al (1995) and others (Gisbert et al 1997; Treiber & Lambert 1998), who reported the importance of *H. pylori* infection in gastric ulcer healing. Our endoscopic findings for slow ulcer healing are similar to those in previous reports (Choi et al 1994; Tunis et al 1997). However, the results of multivariate analysis (Table 2) reveal that the drug (proton pump inhibitor or H_2-receptor antagonist) used for treatment was the most important factor for predicting ulcer healing within eight weeks. This led us to another series of analyses in which risk factors for slow healing were evaluated separately in the groups treated with an H_2-receptor antagonist or a proton pump inhibitor (Tables 3–5).

The analysis by the Chi-squared test (Table 4) shows that endoscopic findings, such as ulcer location at angulus, ulcer size (> 2 cm diam.), and linear-type ulcer were significant risks for delaying ulcer healing in both the proton pump inhibitor- and H_2-receptor antagonist-treated groups. However, *H. pylori* infection was found to be a risk only for the H_2-receptor antagonist-treated group. In other words, *H. pylori* may delay ulcer healing when the ulcer is treated with an H_2-receptor antagonist, but not with a proton pump inhibitor. In this study, the healing rate of gastric ulcers treated with a proton pump inhibitor and with *H. pylori*-eradication therapy (Penston 1996) was the same as that treated with a proton pump inhibitor alone (89·3%, Table 4). A multivariate analysis (Table 5) revealed a clearer difference in the risk factors between the H_2-receptor antagonist- and proton pump inhibitor treatment groups.

Proton pump inhibitors suppress acid secretion more strongly than H_2-receptor antagonists (Savarino et al 1993; Takeda et al 1995), and increase mucosal blood flow more than H_2-receptor antagonists (Holm 1988). Omeprazole, a proton pump inhibitor, and its acid degradation products inhibit cytotoxic activity of human natural killer cells in-vitro (Aybay et al 1995). Lansoprazole, another proton pump inhibitor, binds directly to neutrophils, inhibiting neutrophil accumulation and oxygen-derived free radical production from neutrophils (Suzuki et al 1995). This action may reduce neutrophil-dependent gastric mucosal injury associated with *H. pylori* infection. Lansoprazole increases tissue basic fibroblast growth factor and promotes gastric ulcer healing, but an H_2-receptor antagonist, famotidine, does not (Tuji et al 1995). In addition, lansoprazole reportedly has antimicrobial activity against *H. pylori* in-vitro (Figura et al 1997). These effects of proton pump inhibitors may explain their superior efficacy in the treatment of *H. pylori*-positive gastric ulcers.

According to the Chi-squared test and multivariate analysis, major indicators for slow healing of gastric ulcers are morphological features of the ulcer, especially linear-type ulcer. These are the most significant signs for the delay of ulcer healing with both H_2-receptor antagonist and proton pump inhibitor treatments.

We conclude that morphological features detected by endoscopy may provide important information for predicting ulcer healing, and that proton pump inhibitors should be the first choice for gastric ulcer treatment.

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