Kampo medicine (Saiko-keishi-to) affects the susceptibility of *Helicobacter pylori* to antimicrobial agents

Yoshihisa URITA,* Yukihiko NARUKI, Mamoru NISHINO, Hiroshi KOYAMA, Sachio OTSUKA

First Department of Internal Medicine, Toho University School of Medicine

(*Received August 25, 1997. Accepted October 28, 1997.*)

Abstract

The aim of this study was to examine the efficacy and safety of a newly low-dose triple therapy with lansoprazole, clarithromycin, and Kampo medicine (Saiko-keishi-to ; 柴胡桂枝湯) for the treatment of *H.pylori* infection. Methods : Thirty patients with *H.pylori* infection were treated with a new triple therapy (lansoprazole 30 mg once daily for two weeks, clarithromycin 200 mg three times daily for two weeks, Saiko-keishi-to 2.5 g three times daily for months : group A). The other 30 patients were treated with only initial therapy (lansoprazole 30 mg once daily for two weeks, clarithromycin 200 mg three times daily for two weeks : group B). Eradication was defined by finding *H.pylori* infection by neither culture nor histology six months after completion of eradication therapy. Results : Out of 60 *H. pylori*-positive patients entering this study, 12 patients (group A 5, group B 7) dropped out until the follow-up examination six months after the completion of initial therapy. *H.pylori* infection was eradicated in 17 patients (68.0 %) of group A and in five (21.7 %) of group B. In 17 patients of group A with successful eradication of *H.pylori*, there was a significant fall in serum PG I and PG II. Change rates of PG I and PG II before and after treatment in five patients of group B was lower than in the 17 successful patients of group A. A change rate in anti-*H.pylori* antibody titers before and six months after completion of treatment in 17 patients with successful eradication in group A was larger than in five in group B (0.54±0.29 VS 0.73±0.35). Out of 48 patients, 18 (37.5 %) experienced a dry metallic taste, the most frequent side effect, for the first two weeks. Conclusions : We conclude from this study that Kampo medicine (Saiko-keishi-to) affects the susceptibility of *H.pylori* to antimicrobial agents.

Key words Saiko-keishi-to, *Helicobacter pylori*.

Introduction

Helicobacter pylori (*H.pylori*) is known to be the most important cause of chronic active gastritis [1-3] and has a role in the pathogenesis of gastroduodenal ulcers. [4-6] The eradication of *H.pylori* reduces the recurrence rate of gastroduodenal ulcers. [7,8] Although *H.pylori* is sensitive to many kinds of antibiotics *in vitro*, *H.pylori* infection has proven difficult to cure. [9] It is known that triple therapy with bismuth, metronidazole, and tetracycline or amoxyllin is the therapy of choice. [7,8] Although triple therapy is an effective therapy for eradication of *H.pylori*, many patients on such regimens complain of considerable side effects. [7,8] Because neither bismuth salicylate nor bismuth subcitrate can be available in Japan, dual therapy with proton pump inhibitors and antibiotics have been performed. However, the eradication rate of dual therapy is lower than that of triple therapy. [10,11] Therefore, in order to reduce side effects and improve the eradication, rate of *H.pylori*, it is necessary to modify the dual therapy. As Kampo (Japanese herbal) medicines have contributed to the treatment of a variety of gastrointestinal diseases in Japan, we tried to use it for the *H.pylori* eradication therapy. The aim of this study was to examine the efficacy and safety of a newly low-dose triple therapy with lanso-

*〒143 東京都大田区大森西6-11-1
東邦大学医学部第一内科 瓜田純久
6-11-1, Omorinishi, Ota-ku, Tokyo 143, Japan

prazole, clarithromycin, and Kampo medicine (Saiko-keishi-to ; 柴胡桂枝湯) for the treatment of *H.pylori* infection.

Materials and Methods

Patients : In a prospective randomized study, 60 consecutive patients undergoing *H.pylori* eradication therapy entered the study. Thirty patients with *H. pylori* infection were treated with a new triple therapy using Saiko-keishi-to (group A). The other 30 patients were treated with double therapy without Saiko-keishi-to (group B). Twenty-five of 30 group A patients and 23 of 30 group B patients were investigated endoscopically to cure *H.pylori* infection six months after the completion of eradication therapy. Group A consisted of eight patients with gastric ulcer, four with duodenal ulcer, and 13 with functional dyspepsia. They ranged in age from 21 to 77 years (mean age 52.8 years), and consisted of nine men and 16 women. Group B consisted of seven patients with gastric ulcer, five with duodenal ulcer, and 11 with functional dyspepsia. They ranged in age from 33 to 80 years (mean age 58.1 years), and consisted of nine men and 14 women. There was no significant difference between age, sex distribution, and underlying diseases of two groups (Table I). All patients gave their informed written consent for the study.

Table I Basic data of each treatment group

	group A	group B
Patients	25	23
Men/Women	9/16	9/14
Mean age (±S.D.)	52.8±11.9	58.1±14.4
Diagnoses		
Gastric ulcer	8	7
Duodenal ulcer	4	5
Functional dyspepsia	13	11

H.pylori eradication therapy : Patients were randomly assigned to receive either the new triple therapy, using lansoprazole 30 mg once daily for two weeks, clarithromycin 200 mg three times daily for two weeks, and Saiko-keishi-to 2.5 g three times daily for six months (group A), or the initial double therapy for two weeks, using lansoprazole 30 mg once daily for two weeks, clarithromycin 200 mg three times daily (group B) (Fig.1).

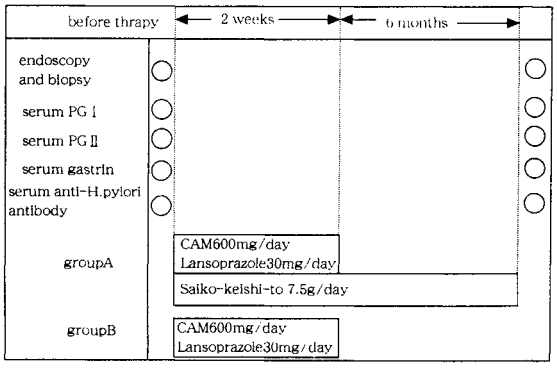

Fig. 1 Therapy regimens of the two study groups

When the ulcer was in the open stage, medical therapy with H2-receptor antagonists (Famotidine 20 mg twice daily) had been performed for six weeks. After that eradication therapy was carried out. In patients with functional dyspepsia requiring therapy or with ulcers in the scarring stage, eradication therapy was performed from the beginning.

Endoscopy and biopsy : Both before eradication therapy and six months after the completion of initial eradication therapy, patients were investigated endoscopically with taking of two antrum, one lower body, two upper body, and cardia biopsy specimens on the greater curvature using different forceps (Fig. 1). Four biopsy specimens taken from each site were cultivated in Belo-Horizonte medium with the selective supplement of Skirrow (Nikken Biomedical Laboratory, Kyoto), and two biopsy specimens taken from the antrum and upper body were analyzed by histology after Giemsa stain. Eradication was defined by finding *H.pylori* infection by neither culture nor histology.

Serology : Blood was taken from all patients after an overnight fast for estimation of basal plasma gastrin, serum pepsinogen I (PG I) and pepsinogen II (PG II) concentration before and after treatment (Fig. 1).

Statistical analyses : Data are presented as mean± S.D. Statistical analyses were performed by qui-square test to compare *H.pylori* eradication rates of the two groups. Student's *t* test was used to examine

the relationship between serum PG I, PG II, PG I/PG II ratio, and gastrin, and the results of *H.pylori* eradication therapy in two groups. A p value<0.05 was considered significant.

Results

Subjects

Out of 60 *H.pylori*-positive patients entering this study, 12 patients dropped out until the follow-up examination six months after the completion of initial therapy (Fig. 2). Nausea prevented one patient from completing the course of treatment during the initial therapy. The other 11 patients did not come to the hospital for unknown reasons (Fig. 2) and follow-up examination could not be performed.

H.pylori eradication

H.pylori infection was eradicated in 17 patients (68.0 %) of group A and in five (21.7 %) of group B (Fig. 2). The eradication rate of *H.pylori* in group A was significantly higher than that of group B.

Serum pepsinogen and gastrin

In 17 patients of group A with successful eradication of *H.pylori*, there was a significant fall in serum PG I from a pretreatment value of 45.9±28.9 ng/ml to a posttreatment value of 29.5±13.6 ng/ml and in serum PG II from 23.9 ng/ml to 7.7±3.3 ng/ml (Table II). By contrast, although in five patients of group B

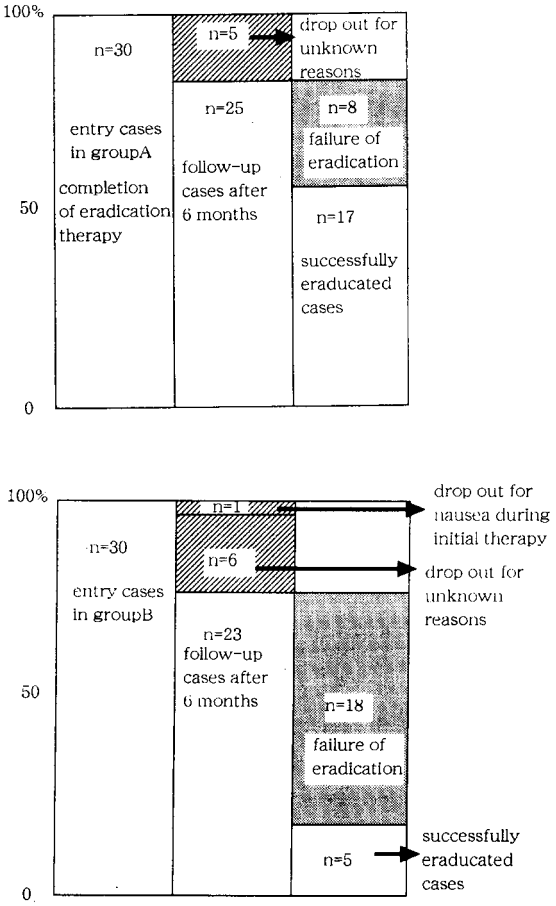

Fig. 2 Results of eradication therapy in group A (Fig. 2a) and group B (Fig. 2b).

Table II Overview of treatment results

	group A		group B	
	Hp (−) after therapy	Hp (+) after therapy	Hp (−) after therapy	Hp (+) after therapy
PG I (ng/ml)				
before therapy	45.9±28.9	55.3±16.3	50.8±18.7	59.0±21.5
after therapy	29.5±13.6 *	64.0±11.8	49.8±21.7	61.5±25.8
		*		
PG II (ng/ml)				
before therapy	23.9±8.9 **	17.5±4.6	20.7±9.9	22.2±9.2
after therapy	7.7±3.3 *	19.2±4.6	11.6±9.4	19.9±10.3
PG I/PG II				
before therapy	2.11±1.06 *	3.20±0.72	2.93±1.63	3.14±1.95
after therapy	3.94±1.46	3.41±0.66	5.19±1.80 **	3.49±1.29
gastrin				
before therapy	162.5±80.3 **	107.9±46.2	186.4±137.1	124.8±59.2
after therapy	147.5±69.6 *	96.8±20.0	66.4±43.7 **	125.9±61.6

*$p<0.01$ **$p<0.05$

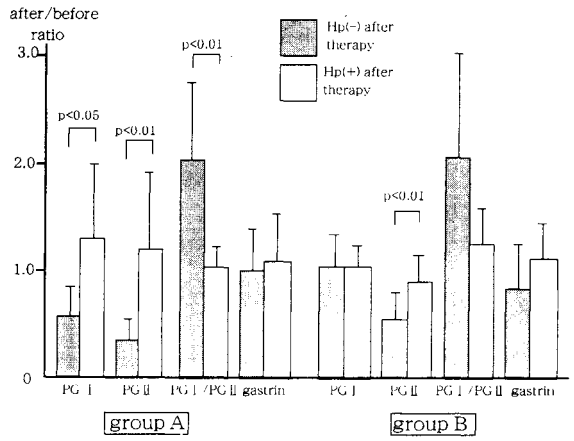

Fig. 3 Changes in serum levels of PG I, PG II, PG I/PG II ratio, and gastrin before and 6 months after the completion of eradication therapy.

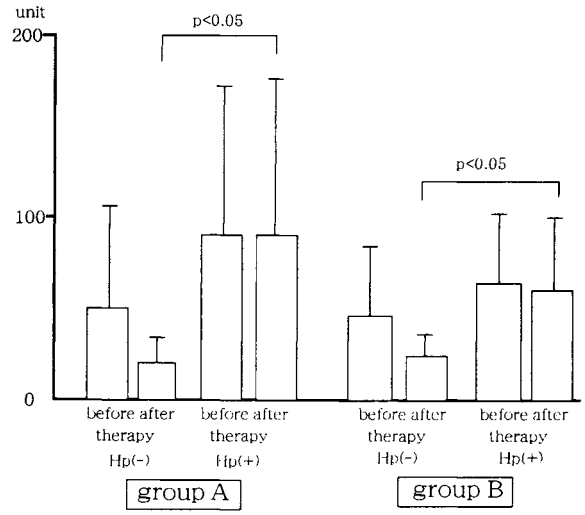

Fig. 4 Changes of serum anti-*Helicobacter pylori* antibody titers before and 6 months after the completion of eradication therapy.

H.pylori was eradicated after treatment, serum PG I did not change before and after treatment, and serum PG II decreased from a pretreatment value of 20.7±9.9 ng/ml to a posttreatment value of 11.6±9.4 ng/ml (Table II). A change rate of PG II before and after treatment in five patients of group B was lower than in 17 successful patients of group A (Fig. 3). In eight patients of group A and 18 patients of group B in whom *H.pylori* had not been eradicated, serum PG I increased after treatment and serum PG II was nothing but a slight decrease (Table II).

Generally speaking, PG I/PG II ratio increased after treatment regardless of *H.pylori* eradication. PG I/PG II ratio before treatment in 17 patients, in whom *H.pylori* was eradicated successfully, of group A was lower than in eight patients (Table II).

Serum levels of gastrin in 17 patients of group A with successful eradication of *H.pylori* before and after therapy were 162.5±80.3 pg/ml and 147.5±69.6 pg/ml, respectively. Those in eight patients with the failure of eradication before and after therapy were 107.9±46.2 ng/ml and 96.8±46.2 ng/ml, respectively. Both before and after treatment those of serum gastrin in group A in whom *H.pylori* was successfully eradicated showed atendency to be higher than that of those in whom *H.pylori* was failed to be eradicated. Those in five patients of group B with successful eradication of *H.pylori* after therapy were 66.4±43.7 pg/ml and lower than those in 18 patients in whom *H. pylori* was failed to be eradicated (Table II).

Serum anti-H.pylori antibody

In the patients with successful eradication of *H. pylori* there was a fall in serum antibody titer against *H.pylori* more than in the patients without eradication six months after treatment as a matter of course (Fig. 4). A change ratio in anti-*H.pylori* antibody titers before and six months after the completion of treatment in 17 patients with successful eradication in group A was larger than in five in group B (0.54±0.29 VS 0.73±0.35).

Side effects

Adverse events occurred in 19 (31.7 %) of 60 subjects who entered in this study. Nausea prevented one patient from completing the course of treatment during the initial therapy (Fig. 2). The other 18 patients who experienced side effects could complete the regimen. A dry metallic taste for first two weeks was reported by 8/25 (32.0 %) and 10/23 (43.8 %) of the subjects in group A and group B, respectively. In all 18 patients taste disturbance resolved within days of finishing the initial treatment of taking clarithromycin.

Discussion

Eradication rates for the organism with triple

therapy vary more than 80 % in previous studies.[10-13] In Japan neither bismuth salicylate nor bismuth subcitrate, important components of most regimens, is available, therefore, we had to conceive another therapy. Although dual therapies with proton pump inhibitors and antibiotics have been performed, eradication rate of dual therapy is lower than that of triple therapy.[10-13] On the othe hand, although triple therapy is effective therapy, many patients on such regimens complain of considerable side effects.[7,8] In order to reduce side effects and improve the eradication rate of *H.pylori*, it is necessary to modify the dual therapy.

It is easy to reduce the quantity of dosage of drugs to reduce side effects. But low dosage of drugs could not be so effective for eradicating *H.pylori* as high dosage as a matter of course. Conversely, the higher dosage of drugs, the more frequently patients complain of a variety of side effects. Then, we tried to develop a new therapy for eradicating *H.pylori* which was more effective with fewer side effects.

Clarithromycin is a new macrolide antibiotic and is more acid stable than erythromycin with similar antimicrobial spectrum. It has excellent *in vitro* activity against *H.pylori* and was reported to be the most effective anti-*H.pylori* drug available at present.[14,15] But it is not sufficient to be used as monotherapy even if patients take such a high dosage of clarithromycin as 500 mg four times daily.[16] Furthermore, the higher the dosage of clarithromycin taken, the more frequently patients experienced taste pervasion.[16] It was thought that we had better not increase a dosage of antimicrobial agent but use plural kinds of anti-*H. pylori* drugs. Then, we decided that clarithromycin used was 200 mg three times daily, and that proton-pump inhibitor and Kampo medicine was used at the same time, expecting the reduction of side effects and the increase of the eradication rates for *H.pylori*. In this study, taste pervasion occurred in group A (32.0 %) less frequently than in group B (43.8 %) and in subjects (75.0 %) who were reported to take a high dosage of clarithromycin such as 500 mg four times daily.[16]

Proton pump inhibitor had been used as one of polychemotherapy drugs for eradicating *H.pylori* for several reasons. It was reported to suppress *H.pylori* directly,[17-19] and to enhance the antimicrobial efficacy *in vivo* after induction of hypoacidity.[20] Because the MIC values of lansoprazole were lower than that of omeprazole,[21] lansoprazole was selected in our regimens instead of omeprazole. In addition, proton pump inhibitors had been used for treatment of ulcer diseases. Therefore, we chose lansoprazole as one drug of new regimens expecting that both ulcer diseases and functional dyspepsia were improved after treatment even if new regimen therapies failed to eradicate *H.pylori*.

On the other hand, eradication rate was achieved in 78 % four weeks after completion of the dual therapy with clarithromycin and omeprazole even if a high dosage of clarithromycin 500 mg three times daily and omeprazole 40 mg daily were used.[15] In Japan clarithromycin is commonly used at a dose of 200 mg twice or three times daily for the treatment of upper and lower respiratory tract infections. If patients take a higher dose of clarithromycin, most of them experience taste perversion.[16] In order to reduce side effects, raise compliance with drugs, popularize the new regimen, and still be safe, we decided that the doses of all drugs of new regimens were limited to common doses in Japan. Instead of decreasing doses of proton pump inhibitor and antibiotics, one more drug, Kampo medicine (Saiko-keishi-to), was added to a new regimen to be more effective with fewer side effects.

Kampo (Japanese herbal) medicines have contributed to the treatment of various diseases in Japan, however, their active principles have not been well understood. Recently, the usefulness of herbal medicines for eradicating *H.pylori* was reported. For example, plaunotol from Plau-noi have an antibacterial activity on *H.pylori*[22] and ecabet sodium from Pini Resina inhibits urease activity of *H.pylori* in acidic condition.[23]

Saiko-keishi-to has been used for treatment of ulcer disases in Japan. Saiko-keishi-to is a mixture of Bupleuri radix (5.0 g/day), Cinnamomi cortex (2.0 g/day), Paeoniae radix (6.0 g/day), Zingiberis rhizoma (4.0 g/day), Glycyrrhizae radix (1.5 g/day), Ginseng radix (3.0 g/day), Scutellariae radix (3.0 g/day), Pinelliae tuber (5.0 g/day) and Zizyphi fructus (4.0 g/day). Bupleuri radix has been used for treatment of hepatitis in Japan. Saikosaponin, one of the main

components of Bupleuri radix, has an effect on inhibiting stages of acute inflammation.[24] Cinnamomi cortex and its main component, cinnamic aldehyde, have been reported to have anti-pyretic, anti-inflammatory, anti-platelet aggregatory, and vasodilatatory action, through suppressing arachidoic acid metabolism.[25] Paeoniflorin, one of the main components of Paeoniae radix, induced the depolarization of resting membrane potentials and the inhibition of acetylcholine potentials.[26] And Paeoniae radix were reported to inhibit the growth of *H.pylori in vitro.*[27] Zingiberis rhizoma was reported to suppress Type 4 allergic reaction.[28] Glycyrrhizae radix also induced the depolarization of resting membrane potentials and the inhibition of acetylcholine potentials [26] and have antiulcer activities by strengthening some gastric mucosal defensive mechanism through prostagrandins reaction.[29] Ginseng radix was reported to stimulate gastric and intestinal motility and central nervous system, and to depress arterial blood pressure.[30] Scutellariae radix and its main component, baicalein, suppress the anaphylactic mediator release. Part of the chemical structure of baicalein is common to that of disodium cromoglycate which is used as an anti-asthmatic agent in Western medicine.[24] Pinelliae tuber have antiulcer activities through its cytoprotective action.[31] Zizyphi fructus has been used in prescriptions treating asthma, allergic rhinitis and even the common cold because a large amount of cyclic AMP as well as a beta-adrenoceptor stimulator was found in Zizyphi fructus.[24]

Saiko-keishi-to is one of the Kampo medicines reported to suppress *H.pylori* directly,[32] so it was considered that each pharmacological action of nine herbal medicines made antiulcer actions mutually and/or independently. Because of Saiko-keishi-to with various anti-ulcer and anti-*H.pylori* actions, we chose it as the third drug of a new regimen.

In this study, the eradication rate of *H.pylori* in group A (Kampo group) was significantly higher than in group B. The results showed us that Saiko-keishi-to was an effectual drug for *H.pylori* eradication therapy through some mechanisms.

Although various diagnostic methods were used for detecting *H.pylori,* eradication was defined by finding *H.pylori* infection by neither culture nor histology after therapy. Because these methods need gastric biopsy specimens, false-negative results are possible. Then an alternative method, which does not need biopsy specimens, should be perfomed at the same time. Serology ia a non-invasive and simple method and a decrease in serum antibody titer is reported to be useful for evaluating *H.pylori* eradication.[33] In addition, using blood samples, we can estimate serum PG I and PG II, in which eradication of *H. pylori* resulted in a fall.[34] In 17 patients of group A with successful eradication of *H.pylori,* there was a significant fall in serum PG I and PG II. By contrast, although in five group B patients *H.pylori* was eradicated after treatment, serum PG I did not change before and after treatment, and the change rate of PG II before and after treatment in five patients of group B was lower than in 17 successful patients of group A. These results indicate that five patients with successful eradication of *H.pylori* in group B might consist of some false-negative patients and its possibility should be higher in group A. It was suggested that eradication in group A was achieved more certainly than in group B. In order to clarify that point, a further follow-up period is required.

On the other hand, a change rate in anti-*H.pylori* antibody titers before and six months after the completion of treatment in 17 patients with successful eradication in group A was larger than in five in group B. A break point of 50 % reduction in antibody titer was reported to indicate bacterial eradication six weeks after the begining of the therapy.[35] A change rate in anti-*H.pylori* antibody was 0.54 ± 0.29 in patients with successful eradication in group A and was lower than in group B. This result also indicated that eradication in group A was achieved more certainly than in group B.

Out of 48 patients, 18 (37.5 %) experienced a dry metallic taste for the first two weeks. This side effect occurred less frequently than reported.[15] The frequencies of a dry metallic taste was thought to decrease because of a lower dose therapy in this regimen. Although a lower dose therapy was feared to decrease the eradication rates, as mentioned above, by adding Saiko-keishi-to to the regimen of *H.pylori* eradication therapy, eradication rates became higher significantly.

We conclude from this study that Kampo medicine (Saiko-keishi-to) affects the susceptibility of *H. pylori* to antimicrobial agents.

和文抄録

Helicobacter pylori (*H. pylori*) 除菌のためのランソプラゾール，クラリスロマイシン，柴胡桂枝湯を用いた新しい低用量の3剤療法を行い，その有用性と安全性について検討した。30例は新3剤療法（ランソプラゾール30 mg 1日1回2週間，クラリスロマイシン200 mg 1日3回2週間，柴胡桂枝湯2.5 g 1日3回6カ月：A群）を，他の30例は最初の2週間の治療（ランソプラゾール30 mg 1日1回，クラリスロマイシン200 mg 1日3回：B群）のみ行った。除菌は除菌治療終了から6カ月後に内視鏡検査を施行し，生検組織の鏡検および組織培養検査で判定した。6カ月後の除菌判定までに12例（group A 5例，group B 7例）が脱落した。A群は17例（68.0％），B群は5例（21.7％）が除菌に成功した。除菌成功したA群の17例は血清ペプシノゲン（PG）I，IIが有意に低下した。除菌成功したB群の5例も低下したが，その変化はA群よりも少なかった。治療後6カ月の血清抗Hp抗体価の低下は，A群がB群よりも有意に多かった。除菌判定を行うことができた48例中，最も多かった副作用は最初の2週間にみられた味覚傷害で，18例（37.5％）に出現した。柴胡桂枝湯は *H.pylori* の抗生剤に対する感受性に影響を及ぼすものと思われた。

References

1) Graham, D.Y.: Campylobacter pylori and peptic ulcer disease. *Gastroenterology* **96**, 615-625, 1989.
2) Rauws, E.A., Langenberg, W., Houthoff, H.J., *et al.*: Campylobacter pyloridis-associated chronic active antral gastritis : A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. *Gastroenterology* **94**, 33-40, 1988.
3) Blaser, M.J.: Gastric Campylobacter-like organisms, gastritis, and peptic ulcer disease. *Gastroenterology* **93**, 371-383, 1987.
4) Labenz, J., Borsch, G.: Evidence for the essential role of Helicobacter pylori in gastric ulcer disease. *Gut* **35**, 19-22, 1994.
5) Goodwin, C.S.: Duodenal ulcer, Campylobacter pylori, and the "leaking roof" concept. *Lancet* **2**, 1467-1469, 1988.
6) Dixon, M.F.: Helicobacter pylori and peptic ulceration : Histological aspects. *J. Gastroenterol Hepatol* **6**, 125-130, 1991.
7) Graham, D.Y., Lew, G.M., Klein, P.D.: Effect of treatment Helicobacter pylori infection on the long term recurrence of gastric and duodenal ulcer. *Ann Intern Med* **116**, 705-708, 1992.
8) Marshall, B.J., Goodwin, C.S., Warren, J.R.: Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. *Lancet* **2**, 1437-1441, 1988.
9) Glupczynski, Y., Burette, A.: Drug therapy for Helicobacter pylori infection : Problem and pitfalls. *Am J Gastroenterol* **85**, 1545-1551, 1990.
10) Forne, M., Viver, J.M., Espinos, J.C., Coll, I., Tressera, F., Garau, J.: Impact of colloidal bismuth subcitrate in the eradication rates of Helicobacter pylori infection-associated duodenal ulcer using a short treatment regimen with omeprazole and clarithromycin : A randomized study. *Am J Gastroenterol* **90**, 718-721, 1995.
11) Labenz, J., Gyenes, E., Ruhl, G.H., Borsch, G.: Omeprazole plus amoxicillin : Efficacy of various treatment regimens to eradicate Helicobacter pylori. *Am J Gastroenterol* **88**, 491-495, 1993.
12) Chiba, N., Rao, B.V., Rademmaker, J.W., *et al.*: Meta-analysis of the efficacy of antibiotic therapy in eradicating Helicobacter pylori. *Am J Gastroenterol* **87**, 1716-1726, 1992.
13) Cutler, A.F., Schubert, T.T.: Patient factors affecting Helicobacter pylori eradication with triple therapy. *Am J Gastroenterol* **88**, 505-509, 1993.
14) Graham, D.Y., Operkun, A.R., Klein, P.D.: Clarithromycin for the eradication of Helicobacter pylori. *J Clin Gastroenterol* **16**, 292-294, 1993.
15) Logan, R.P.H., Gummett, P.A., Schaufelberger, H.D., *et al.*: Eradication of Helicobacter pylori with clarithromycin and omeprazole. *Gut* **35**, 323-326, 1994.
16) Peterson, W.L., Graham, D.Y., Marshall, B., *et al.*: Clarithromycin as monotherapy for eradication of Helicobacter pylori : A randomized, double-blind trial. *Am J Gastroenterology* **88**, 1960-1964, 1993.
17) Sharp, J., Logan, R.P.H., Walker, M.M., Gummett, P.A., Missiewicz, J.J., Baron, J.H.: Effect of omeprazole on Helicobacter pylori. *Gut* **32**, A565, 1991.
18) Stolte, M., Bethke, B.: Elimination of Helicobacter pylori under treatment with omeprazole. *Z Gastroenterol* **28**, 271-274, 1990.
19) Graham, D.Y., Klein, P.D., Opekun, A.R., *et al.*: In vitro susceptibility of Campylobacter pylori. *Am J Gastroenterol* **84**, 233-238, 1989.
20) Urge, P., Olsson, J., Gad, A., *et al.*: Does omeprazole (40 mg O.M.) improve antimicrobial therapy directed towards gastric Campylobacter pylori in patients with antral gastritis? A pilot study. In : Megraud, F., Lamouliatte, H., eds. Gastroduodenal pathology and Campylobacter pylori. Amsterdam : Elsevier, 641-645, 1989.
21) Iwahi, T., Satoh, H., Nakao, M., *et al.*: Lansoprazole, a novel benzimidazole proton pump inhibitor and its related compounds, have selective activity against Helicobacter pylori. *Antimicrob Agents Chemother* **35**, 490-496, 1991.
22) Karita, M., Morshed, M.G., Ouchi, K., *et al.*: Bismuth-free triple therapy for eradicating Helicobacter pylori and reducing the gastric ulcer recurrence rate. *Am J Gastroenterol* **89**, 1032-1035, 1994.
23) Onoda, Y., Magaribuchi, T., Tamaki, H.: Effects of 12-sulfodehydroabietic acid monosodium salt (TA-2711), a new antiulcer agent, on gastric secretion and experimental ulcer in rat. *Japan J Pharmacol* **51**, 65-73, 1989.
24) Cyong, J.: A pharmacological study of the anti-inflammatory activity of Chinese herbs. A review. *Acupuncture & Electro-Therapeutics Res., Int. J.* **7**, 173-202, 1982.
25) Takenaga, M., Hirai, A., Tareno, T., *et al.*: In vitro effect of cinnamic aldehyde, a main component of cinnamomi cortex, on human platelet aggregation and arachidonic acid metabolism. *J. Pharmacobio-Dyn.* **10**, 201-208, 1987.
26) Kimura, M., Kimura, I., Nojima, H.: Depolarizing neuromuscular

blocking action induced by electropharmacological coupling in the combined effect of paeoniflorin and glycyrrhizin. *Jap. J. Pharmacol* **37**, 395-399, 1985.

27) Imamura, L., Tsuchiya, M., Inada, A., Nakanishi, T., and Kobashi, K.: Inhibition of urease and growth of Helicobacter pylori by herb extracts. *J Teaditional Med* **12**, 129-136, 1995.

28) Nishiyori, T.: Effect of Chinese blended medicine, Saiboku-to, on Type 4 allergic reaction. *Jpn. J. Allergol.* **32**, 317-323, 1983.

29) Yano, S., Harada, M., Watanabe, K., *et al.*: Antiulcer activities of glycyrrhetinic acid derivatives in experimental gastric lesion models. *Chem. Pharm. Bull.* **37**, 2500-2504, 1989.

30) Takagi, K., Saito, H., Nabata, H.: Pharmacological studies of Panax Ginseng root: Estimation of pharmacological actions. *Jap. J. Pharmacol* **22**, 245-259, 1972.

31) Watanabe, K., Shibata, M., Yano, S., *et al.*: Antiulcer activity of extracts and isolated compounds from Zedoary (Gashutsu) cultivated in Yakushima. *Yakugaku Zasshi* **106**, 1137-1142, 1986.

32) Shimoyama, T., Fukuda, Y., Tonokatsu, Y., Abo, H.: Helicobacter pylori and gastric mucosa. *J Japan Soc Int Med* **82**, 286-292, 1993.

33) Culter, A., Schbert, A., Schbert, T.: Role of Helicobacter pylori serology in evaluating treatment success. *Dig. Dis. Sci.* **38**, 2262-2266, 1993.

34) Chittalallou, R.S., Dorrian, C.A., Ardill, J.E.S., *et al.*: Effect of Helicobacter pylori on serum Pepsinogen I and plasma gastrin in duodenal ulcer patients. *Scand J Gastroenterol* **27**, 20-24, 1992.

35) Hirschl, A.M., Brandstatter, G., Dragosics, B.: Kinetics of specific IgG antibodies for monitoring the effect of anti-Helicobacter pylori chemotherapy. *J Infect Dis* **168**, 763-766, 1993.