Journal of Gastroenterology and Hepatology (1999) **14**, 495–499

OESOPHAGOGASTROINTESTINAL DISEASES

Rebamipide prevents occurrence of gastric lesions following transcatheter arterial embolization in the hepatic artery

HIDEYUKI NOMURA,* KATSUHISA MIYAKE,* RYOSUKE HIRAKATA,† SHINOBU MIGITA,‡ OSAMU OKAMOTO* AND GENJI SHIRAISHI*

*Departments of *Internal Medicine, †Radiology and ‡Clinical Laboratory, Shin-Kokura Hospital, Kanada, Kitakyushu, Japan*

Abstract

Background:Transcatheter arterial embolization (TAE) of the hepatic artery is a common treatment method for hepatocellular carcinoma (HCC), but it often induces gastric mucosal injury. We examined whether or not rebamipide administration, beginning 1 week before and ending 2 weeks after TAE, can prevent worsening of gastric mucosal disorders.

Methods: The subjects were 73 chronic hepatitis C or type C liver cirrhosis patients who concomitantly had HCC and received TAE in our hospital. The patients were randomly allocated to the rebamipide group (oral, 300 mg/day for 3 weeks starting 1 week before TAE) or the non-rebamipide group. Gastric endoscopy was performed 1 week before and 2 weeks after TAE and the presence of erythema, erosion and/or submucosal haemorrhagic spots was monitored. Based on the findings, gastric mucosal disorder before and after TAE was quantitatively evaluated using the modified Lanza score (MLS).

Results: Overall, MLS after TAE increased significantly ($P < 0.05$). However, in the rebamipide group, MLS did not change. The MLS after TAE increased significantly in patients who had either liver cirrhosis, oesophageal varices or gastropathy ($P < 0.01$ or < 0.05). In the non-rebamipide group, a significant increase in MLS after TAE was observed in patients who had one of the above-mentioned three diseases ($P < 0.01$ or < 0.05).

Conclusions: Gastric lesions which were present before TAE were significantly worsened after TAE. Rebamipide administration prevents TAE-induced aggravation of gastric lesions.

Key words: gastric lesion, rebamipide, transcatheter arterial embolization.

INTRODUCTION

With the recent increase in hepatocellular carcinoma (HCC), various treatment methods have been investigated. Transcatheter arterial embolization (TAE) of the hepatic artery is one of these therapies. It has been commonly applied and its clinical efficacy has been proven. However, TAE also induces various complications.[1–4] For example, embolization of the hepatic artery results in tumour necrosis, which then induces congestion of the gastric artery and the portal vein, which reduces blood flow in the gastric mucosa and finally induces such disorders as haemorrhagic gastritis and gastric ulcer. Lau *et al.* reported occurrence of acute gastric pain after TAE.[5]

In the present study, we administered the gastroprotective agent, rebamipide (Mucosta®; Otsuka Pharmaceuticals, Tokyo, Japan), to chronic hepatitis C or type C liver cirrhosis patients who developed HCC and who were scheduled to have TAE. Rebamipide is a registered drug in Japan and is as commonly prescribed as the sucralphate in treatment for gastric ulcer and chronic gastritis.

METHODS

Patients

The subjects were 73 patients with chronic hepatitis C or type C liver cirrhosis who developed HCC and who

Correspondence: Hideyuki Nomura, Department of Internal Medicine, Shin-Kokura Hospital, 1-3-1, Kanada, Kokurakita-ku, Kitakyushu 803-8505, Japan.

Accepted for publication 5 August 1998.

underwent TAE in Shin-Kokura Hospital. They consisted of 52 males and 21 females: 14 chronic hepatitis C and 59 type C liver cirrhosis cases (age range 43–78 years, mean age 63.2 years). They were enrolled in this study between January 1996 and March 1997 and, at that time, they were randomly allocated to either the rebamipide group or the non-rebamipide group using the envelope method. Those patients who regularly consumed alcohol or who had a history of gastric or duodenal ulcer were excluded from the study. All the 14 chronic hepatitis C patients had received a liver biopsy and their Knodell scores[6] were 12 or higher. Among the 59 cirrhosis patients, 26 had received a liver biopsy and they were histologically diagnosed as having type C liver cirrhosis. The remaining 33 patients did not receive a biopsy and they were diagnosed as having cirrhosis based on clinical findings.

This study was approved by the Ethics Committee of Shin-Kokura Hospital. All patients gave informed consent to participate in this study. All procedures were conducted in accordance with the Helsinki Declaration of 1975 (revised in 1983) and all laboratory work was done in Shin-Kokura Hospital.

Rebamipide administration

Patients in the rebamipide group received 300 mg/day rebamipide for 3 weeks from 1 week before TAE to 2 weeks after TAE. The patients were prohibited from taking other gastroprotective agents and/or anti-ulcer medicines during the study period.

Gastric endoscopy

Gastric endoscopy was performed 1 week before and 2 weeks after TAE in order to monitor the presence of oesophageal varices, and erythema, erosion and/or submucosal haemorrhage on the antrum and corpus of the stomach. At the first endoscopy, biopsy samples were obtained from the antrum and the corpus of all subjects for histological examination. Patients were evaluated as gastropathy-positive, if they (i) had portal hypertension and gastric lesion(s) (i.e. erythema, erosions and/or submucosal haemorrhage); and (ii) were histologically confirmed to have no or slight inflammatory cell infiltration but had changes in the mucosal and submucosal vascular architecture (e.g. dilated veins, ectatic capillaries, thickening of arterioles and submucosal arteriovenous communications).[7]

Helicobacter pylori examination

With the biological specimens obtained from the antrum and corpus at the initial gastric endoscopy, *H. pylori* infection was examined using rapid urease test kits (CLO test™, Delta West Co. Ltd, Western Australia, Australia).[8]

Other examinations

At the time of hospital admission, all patients received abdominal ultrasonography and computed tomography (CT) and the number of tumour nodules and the maximum diameter of the tumour were measured. Before and 2 weeks after TAE, total protein (TP), albumin (Alb), alanine aminotransferase (ALT) and lactic dehydrogenase (LDH) were measured.

Transcatheter arterial embolization

Transcatheter arterial embolization was performed according to the Seldinger method:[9] a guidewire followed by a catheter was inserted percutaneously into the femoral artery of the patient while under local anaesthesia, 1–2 mm cubes of gelatin sponge were injected into the area between the periphery of the proper hepatic artery and the target tumour and the arterial flow was blocked. In the present study, we first injected 30 mg doxorubicin and 6 mL lipiodol and then injected the gelatin sponge containing 10 mg mytomycin C for embolization. Angiograms of the hepatic artery were simultaneously obtained.

Quantification of gastric mucosal disorder by modified Lanza score

As shown in Table 1, the severity of the gastric mucosal disorder was evaluated by a grade based on the number of gastric lesions and the summation of the grade was used as the modified Lanza score (MLS).[10]

Patient background

Table 2 summarizes the patient background in each group. Before TAE, there were no significant group differences for gender, mean age, liver tissue type, presence or absence of oesophageal varices or gastropathy,

Table 1 Modified Lanza scores

Lesion	Grade
No erythema	0
Presence of erythema	1
No submucosal haemorrhage	0
1–4 submucosal haemorrhagic spots	1
5–10 submucosal haemorrhagic spots	2
11–20 submucosal haemorrhagic spots	3
Confluent haemorrhage	4
No erosion	0
1–4 erosions	2
5–10 erosions	3
11–20 erosions	4

Table 2 Patient background

	Rebamipide group ($n=37$)	Non-rebamipide group ($n=36$)
Gender		
Male	25 (68)	27 (75)
Female	12 (32)	9 (25)
Mean age (years)	63.5	62.9
Chronic hepatitis	8 (22)	6 (17)
Liver cirrhosis	29 (78)	30 (83)
Presence of oesophageal varix	19 (51)	20 (56)
Presence of gastropathy	22 (59)	22 (61)
H. pylori infection		
Positive	9 (24)	7 (19)
Negative	28 (76)	29 (81)
Maximum tumour diameter (cm)	2.8	2.4
No. HCC nodules	2.8	3.4

Figures in parentheses are percentages. *H. pylori*, *Helicobacter pylori*; HCC, hepatocellular carcinoma.

H. pylori infection, maximum tumour diameter and number of HCC nodules.

RESULTS

Gastric symptoms and ulcers after transcatheter arterial embolization

Within 1 week after TAE, fever occurred in 68 patients (93%); epigastralgia in 56 (77%); nausea in 59 (81%); and anorexia in 39 (53%). Nausea occurred in 23 rebamipide patients (70%) and in 33 non-rebamipide patients (92%) and there was a significant group difference ($P<0.05$). However, there was no difference in the frequency of the other symptoms between the groups. Ulcers were not detected by gastric endoscopy after TAE in either group.

Modified Lanza score before and after transcatheter arterial embolization

Overall, MLS significantly increased after TAE ($P<0.05$). In the rebamipide group, MLS did not change, whereas it increased significantly after TAE in the non-rebamipide group ($P<0.05$) and in the patients with oesophageal varices ($P<0.05$), liver cirrhosis ($P<0.05$) or gastropathy ($P<0.01$; Table 3). *Helicobacter pylori* infection, tumour size and tumour number did not influence MLS after TAE. The 20 patients who did not have gastric mucosal disorder before TAE did not develop any gastric disorders after TAE, regardless of rebamipide administration.

Presence of gastropathy was confirmed by gastric endoscopy before TAE in 44 of 53 patients with gastric mucosal disorder (83%), 43 of 59 liver cirrhosis patients (73%) and 36 of 39 patients with oesophageal varices (92%).

Table 3 Modified Lanza scores before and after transcatheter arterial embolization (TAE) according to factors examined

	Before TAE	After TAE	*P* value
Rebamipide			
Administered ($n=37$)	3.7 ± 3.0	3.9 ± 3.2	NS
Not administered ($n=36$)	3.6 ± 2.6	5.4 ± 3.9	<0.05
Gender			
Male ($n=52$)	3.4 ± 2.7	4.0 ± 3.7	NS
Female ($n=21$)	4.3 ± 2.7	5.7 ± 2.6	NS
Liver tissue			
Chronic hepatitis ($n=14$)	$1.8\pm2.0^{\dagger}$	2.1 ± 2.2	NS
Liver cirrhosis ($n=59$)	$3.9\pm2.6^{\dagger}$	5.1 ± 3.5	<0.05
Oesophageal varix			
Present ($n=39$)	$5.1\pm2.3^{\dagger}$	6.6 ± 3.3	<0.05
Absent ($n=34$)	$1.8\pm2.0^{\dagger}$	2.0 ± 2.7	NS
Gastropathy			
Present ($n=44$)	$5.1\pm2.2^{\dagger}$	6.6 ± 3.0	<0.01
Absent ($n=29$)	$1.1\pm1.8^{\dagger}$	1.3 ± 2.2	NS
H. pylori infection			
Positive ($n=16$)	$5.3\pm3.2^{\star}$	6.5 ± 4.4	NS
Negative ($n=57$)	$3.0\pm2.3^{\star}$	3.8 ± 3.2	NS
Maximum tumour diameter			
<3 cm ($n=36$)	3.0 ± 2.4	4.0 ± 3.8	NS
≥3 cm ($n=37$)	4.2 ± 2.9	5.1 ± 3.0	NS
No. nodules			
1 or 2 ($n=36$)	3.3 ± 2.7	4.3 ± 3.2	NS
3 or more ($n=37$)	3.7 ± 3.0	4.8 ± 3.6	NS
Total	3.5 ± 2.6	4.6 ± 3.5	<0.05

Figures represent mean ± SE. NS, not significant. $^{\star}P<0.05$ (positive *vs* negative). $^{\dagger}P<0.01$ (chronic hepatitis *vs* liver cirrhosis or present *vs* absent).

The MLS before TAE was significantly higher in liver cirrhosis patients than in chronic hepatitis patients ($P<0.01$); in patients with oesophageal varices than in patients without varices ($P<0.01$); in gastropathy-positive patients than in negative patients ($P<0.01$); and *H. pylori*-infected patients than in negative patients ($P<0.05$).

In the non-rebamipide group, the MLS of patients who had liver cirrhosis, oesophageal varices or gastropathy increased significantly after TAE ($P<0.05$, <0.01, <0.01, respectively; Table 4). In the rebamipide group, MLS increased in patients with these diseases, but the increases were not significant.

Biochemical test results

Overall, test results before TAE were: TP 6.6 g/dL, Alb 4.0 g/dL, ALT 76 IU/L and LDH 388 IU/L. Two weeks

Table 4 Modified Lanza scores before and after transcatheter arterial embolization (TAE) in each group

	Before TAE	After TAE	*P* value
Non-rebamipide group			
Liver cirrhosis ($n=30$)	3.9 ± 2.3	6.0 ± 3.9	< 0.05
Oesophageal varix ($n=20$)	5.1 ± 2.1	7.9 ± 3.2	< 0.01
Gastropathy ($n=22$)	5.0 ± 1.9	7.6 ± 3.0	< 0.01
Rebamipide group			
Liver cirrhosis ($n=29$)	4.0 ± 2.9	4.5 ± 3.3	NS
Oesophageal varix ($n=19$)	5.1 ± 2.8	5.5 ± 2.7	NS
Gastropathy ($n=22$)	5.2 ± 2.4	5.6 ± 2.6	NS

Figures represent mean ± SE. NS, not significant.

after TAE, TP and Alb decreased significantly to 6.3 g/dL ($P<0.01$) and 3.8 g/dL ($P<0.001$), respectively. Alanine aminotransferase and LDH increased to 85 IU/L and 391 IU/L, respectively, but there were no significant differences.

DISCUSSION

It is difficult to quantitatively express gastric mucosal disorders found on gastric endoscopy. Lanza *et al*. tried to evaluate the efficacy of various gastroprotective agents and developed their own scoring system for severity evaluation.[10] Since then, modification of Lanza's scoring method has been commonly used in many studies.[11–14] In the present study, we also used the modified Lanza score[10] in order to quantitatively evaluate the severity of gastric mucosal disorders.

In the present patients, gastric lesions found before TAE were worsened after TAE. In particular, aggravation was significant in the patients who were gastropathy-positive before TAE. However, administration of the gastroprotective agent, rebamipide, prevented the worsening of gastric lesions.

Hepatocellular carcinoma is frequently associated with chronic hepatitis or liver cirrhosis. It has also been reported that gastric mucosal lesions occur frequently in chronic liver disease patients and the lesions are quite remarkable in liver cirrhosis patients with portal hypertension.[15–18] In the classification of chronic gastritis, gastric mucosal disorders caused by portal hypertension are independently categorized into portal hypertensive gastropathy,[19] where gastric endoscopy often reveals erythema, erosion and submucosal hemorrhage.[20] Histologically, gastric lesions of gastropathy-positive patients are associated with no or slight infiltration of inflammatory cells (e.g. lymphocytes and neutrophils) whereas the infiltration is commonly found in chronic gastritis and there are changes in the mucosal and submucosal vascular architectures (e.g. dilated veins, ectatic capillaries, thickening of arterioles and submucosal arteriovenous communications).[7]

In the development of gastric mucosal disorders in chronic liver disease, decreased activity of protective factors rather than the strengthening of challenge factors, plays a major role and such disorders are reported to occur by the following mechanisms: (i) circulatory disorder in gastric mucosa caused by portal hypertension (portal congestion);[15–19] (ii) decreased resistance of gastric mucosa due to systemic nutritional disorder and decreased serum protein; and (iii) decreased prostaglandin E_2 level in gastric mucosa.[15–18] We used a gastroprotective agent, rebamipide, in this study. Rebamipide shows a preventative or healing effect in gastric ulcer models and gastritis models of animals and its efficacy was also confirmed in acute ulcer models.[21,22] It prevents gastric damage by increasing endogenous prostaglandin E_2 levels in the gastric mucosa[23] and cytoprotective effects have also been reported.[24] It is also thought to increase mucosal blood flow in humans. In addition, it has also been shown to inhibit gastric mucosal injury induced by ischaemia-reperfusion,[25] non-steroidal anti-inflammatory drugs[23] and free radicals.[21,26] Free radicals are involved in the establishment of ischaemic gastric mucosal lesions[27] and rebamipide is the only gastroprotective agent that suppresses the production of free radicals.[21,26] The incidence of adverse reactions to rebamipide are very low: among 6275 patients who received rebamipide in clinical trials, 54 adverse events (0.86%) were reported in 43 patients (0.69%) and there has been no specific designation in the symptoms (pers. comm.). Based on its mechanisms of action, we hypothesized that rebamipide could be useful in the prevention of gastric damage following TAE and considered that a 3 week administration, beginning 1 week before TAE and ending 2 weeks after TAE, can prevent development of TAE-induced gastric lesions.

In the present study, gastropathy was positive in more than 70% of our patients who had liver cirrhosis associated with portal hypertension or who had oesophageal varices. In contrast, MLS was significantly high in the patients who had liver cirrhosis with advanced hepatic disorders or who had oesophageal varices caused by portal hypertension. Therefore, gastropathy is related to the progression of liver diseases and/or increase of portal vein pressure.

The significantly higher MLS in *H. pylori*-positive patients also indicated the involvement of *H. pylori* infection in gastric mucosal disorders. However, *H. pylori* infection and the worsening of gastric lesions after TAE were not related.

Patients without gastric lesions before TAE did not develop lesions after TAE. However, in liver cirrhosis patients who had gastric mucosal disorders before TAE and in patients with oesophageal varices or gastropathy, TAE significantly worsened the lesions. Transcatheter arterial embolization also induce transient hepatic insufficiency, which is indicated by the significant decreases in total protein and albumin levels after TAE. A possible reason for this aggravation is that transient hepatic insufficiency and further worsening of gastric mucosal circulation developed after TAE in patients who had circulatory disorders in the gastric mucosa due to pre-existing portal hypertension. Therefore, circulation disorders in the gastric mucosa may be related to the worsening of gastric mucosal disorders after TAE

and the findings of this article indicate that rebamipide administration is worth considering for patients who are to receive TAE.

REFERENCES

1 Matsui O, Kadoya M, Yoshikawa J *et al*. Small hepatocellular carcinoma: Treatment with subsegmental transcatheter arterial embolism. *Radiology* 1993; **188**: 79–83.

2 Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983; **148**: 397–401.

3 Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma: A randomized controlled trial. *Gastroenterology* 1988; **94**: 453–6.

4 Ikeda K, Kumada H, Saitoh S, Arase Y, Chayama K. Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma: An analysis by Cox proportional hazard model. *Cancer* 1991; **68**: 2150–4.

5 Lau GKK, Hui WM, Hu S, Ngan H, Lam SK. Occurrence of acute gastroduodenitis after transcatheter-oily-chemoembolization (TOCE): Role of gastroduodenal microcirculation (Abstract). *Gastroenterology* 1996; **110**: A1246.

6 Knodell RG, Ishak KG, Black WC *et al*. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981; **1**: 141–5.

7 Genecin P, Groszmann RJ. Portal hypertension. In: Schiff L, Schiff ER, eds. *Diseases of the Liver.* Philadelphia: JB Lippincott Co., 1993; 935–73.

8 Marshall BJ, Warren JR, Francis GJ *et al*. Rapid urease test in the management of *Campylobacter pyloridis*-associated gastritis. *Am. J. Gastroenterol.* 1987; **82**: 200–10.

9 Seldinger SI. Catheter replacement of the needle in percutaneous arteriography. *Acta Radiol.* 1952; **39**: 368–76.

10 Lanza FL, Royer GL, Nelson RS. Endoscopic evaluation of the effects of aspirin, buffered aspirin and enteric-coated aspirin on gastric and duodenal mucosa. *N. Engl. J. Med.* 1980; **303**: 136–8.

11 McAlindon ME, Muller AF, Filipowicz B, Hawkey CJ. Effect of allopurinol, sulphasalazine and vitamin C on aspirin induced gastroduodenal injury in human volunteers. *Gut* 1996; **38**: 518–24.

12 Murray FE, Hudson N, Atherton JC, Cole AT, Scheck F, Hawkey CJ. Comparison of effects of calcium carbasalate and aspirin on gastroduodenal mucosal damage in human volunteers. *Gut* 1996; **38**: 11–14.

13 Stachura J, Konturek JW, Denbinski A, Domschke W. Do infiltrating leukocytes contribute to the adaptation of human gastric mucosa to continued aspirin administration? *Scand. J. Gastroenterol.* 1994; **29**: 966–72.

14 Konturek JW, Dembinski A, Stoll R, Konturek M, Domschke W. Gastric mucosal blood flow and neutrophil activation in aspirin-induced gastric mucosal damage in man. *Scand. J. Gastroenterol.* 1993; **28**: 767–71.

15 McCormack TT, Sims J, Eyre-Brook I *et al*. Gastric lesions in portal hypertension: Inflammatory gastritis or congestive gastropathy. *Gut* 1985; **26**: 1226–32.

16 Vigneri S, Termini R, Piraino A, Scialabba A, Pisciotta G, Fontana N. The stomach in liver cirrhosis. Endoscopic, morphological and clinical correlations. *Gastroenterology* 1991; **101**: 472–8.

17 Arakawa T, Sato H, Fukuda T, Nakamura H, Kobayashi K. Endogenous prostaglandin E_2 in gastric mucosa of patients with alcoholic cirrhosis and portal hypertension. *Gastroenterology* 1987; **93**: 135–40.

18 Sato T, Imamura M, Sasaki I, Ohneda A. Gastric acid secretion and gastrin and gastric inhibitory polypeptide release in cirrhotic patients. *Am. J. Gastroenterol.* 1985; **80**: 163–9.

19 Tytgat GNJ. The Sydney system: Endoscopic division. Endoscopic appearances in gastritis/duodenitis. *J. Gastroenterol. Hepatol.* 1991; **6**: 223–34.

20 Papazian A, Braillon A, Dupas JL, Sevenet F, Capron JP. Portal hypertensive gastric mucosa: An endoscopic study. *Gut* 1986; **27**: 1199–203.

21 Yamasaki K, Kanbe T, Yabuuchi Y. Inhibition of PAF-induced gastric mucosal lesion in the rat by pramipide (OPC-12759), a novel antiulcer agent: Involvement of oxygen-derived free radicals. *Gastroenterology* 1989; **96**: A556.

22 Okabe S, Hiramatsu Y, Yamasaki K, Sakurai I, Shima T. Effect of rebamipide on HCl-taurocholate-induced gastritis in rats. *Ther. Res.* 1991; **12**: 3253–63.

23 Yamasaki K, Kanbe T, Chijiwa T, Ishiyama H, Morita S. Gastric mucosal protection by OPC-12759, a novel antiulcer compound, in the rat. *Eur. J. Pharmacol.* 1987; **142**: 23–9.

24 Kleine A, Kluge S, Peskar BM. Stimulation of prostaglandin biosynthesis mediates gastroprotective effect of rebamipide in rats. *Dig. Dis. Sci.* 1993; **38**: 1441–9.

25 Naito Y, Yoshikawa T, Matsuyama K *et al*. Effect of rebamipide, a novel anti-ulcer agent, on acute gastric mucosal injury induced by ischemia-reperfusion in rats. *Pathophysiology* 1994; **1**: 161–4.

26 Ogino K, Hobara T, Ishiyama H *et al*. Antiulcer mechanism of action of rebamipide, a novel antiulcer compound, on diethyldithiocarbamate-induced antral gastric ulcer in rats. *Eur. J. Pharmacol.* 1992; **212**: 9–13.

27 Itou M, Guth PH. Role of oxygen derived free radicals in hemorrhagic shock-induced gastric lesions in the rat. *Gastroenterology* 1985; **88**: 1162–7.