ORIGINAL

Evaluation of serum amylase and gabexate mesilate with endoscopic papillary balloon dilatation

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Abstract : Gabexate mesilate (GM) relaxes the papilla of Vater in addition to inhibiting the several proteases. We evaluated whether prophylactic administration of GM would prevent the occurrence of acute pancreatitis in endoscopic papillary balloon dilation (EPBD).

Nineteen patients with common bile duct stones were separated into two groups according to the admission year. The group A has been administered GM intravenously at 2mg/kg/hr after EPBD till six hours later, and the group B has been administered GM before fifteen minutes of EPBD till six hours later.

The mean value of sphincter of Oddi (SO) basal and peak pressure in the group B was significantly lower than that in the group A, moreover the mean value of the pancreatic pressure in the group B was significantly lower than that in the group A. However two cases had mild acute pancreatitis in the group B.

GM loosened SO and pancreatic duct pressure by direct stimulation of SO, although it could not have enough effect to prevent the acute pancreatitis in EPBD. J. Med. Invest. 54 : 65-71, February, 2007

Keywords **:** *endoscopic papillary balloon dilatation, serum amylase, acute pancreatitis, gabexate mesilate*

INTRODUCTION

Endoscopic papillary balloon dilation (EPBD) was reassessed for the effective method for management of common bile duct (CBD) stones in the first half of 1990's (1, 2). And some reports revealed that EPBD was more safe and effective method than endoscopic sphincterotomy (EST). And it is believed that EPBD can preserve sphincter of Oddi (SO) function (3-7). Especially it is reported that EPBD is more safety and easier than EST in patients with the Billroth II anastomosis, the coagulopathy, and the periampullary diverticulum (8-10). However Disario, *et al*. reported the result of the endoscopic balloon dilation compared to sphincterotomy for extraction of bile duct stones (EDES) study. It showed high frequency of acute pancreatitis in EPBD with 15.4% (18 of 117 patients) including 2 deaths compared in EST with 0.8% (1 of 120 patients). They concluded that EPBD should be avoided in routine practice (11).

Then it was thought that the local trauma of the papilla from balloon dilation and/or repeated attempts for extraction of CBD stones would cause the spasm and/or edematous change of the papilla generally (10, 11). Gregg, *et al.* described that the risk of acute pancreatitis became lower as pancreatic duct pressure decreased (12). Then it was reported that the sublingual nitroglycerin tablet, epinephrine irrigation and isosorbide dinitrate drip in-

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fusion the stent placement of pancreatic duct (PD) were effective to decrease the spasm and/or the edematous change of papilla after EPBD (13-16).

In Japan, sometimes Gabexate Mesylate (GM) was administered after EPBD prophylactically. GM has been proved to reduce post-ERCP pancreatitis (17). Additionally GM loosens SO (18). Therefore we evaluated whether prophylactic administration of GM was effective for preventing the acute pancreatitis after EPBD.

PATIENTS AND METHODS

Patients

From August 2000 to December 2002, nineteen consecutive patients with CBD stones examined in our department. There were nine women and ten men. Their mean age was 72 years (range 34-90 years). None of them have undergone an operation of the pancreas or the stomach, and been diagnosed as chronic pancreatitis. The patients were limited to those the major and the minor pancreatic duct assumed the normal form.

Written informed consent was obtained from each patient prior to procedure.

METHODS

We separated the nineteen cases into two groups according to the admission year. The one group was composed of the patients who were admitted from August 2000 to August 2001. And the other group was from September 2001 to December 2002. The former was group A, the latter was group B. The group A has been administered GM intravenously by drip infusion at 2 mg/kg/hr after EPBD till six hours later. The group B has been administered GM as same dose as Group A before fifteen minutes of EPBD till six hours later. The group A included twelve patients. The group B was seven patients. The blood pressure, the heart rate, and the O_2 saturation of all patients were continuously determined by an automatic sphygmomanometer and monitor during EPBD.

Manometry was measured in line with Okazaki methods before endoscopic retrograde cholangiography (ERC) (19). Manometry was performed under pharyngeal anesthesia (lidocaine spray) at the left lateral recumbent position which avoided loading abdominal stress. A 4-French micro transducer catheter (Gaeltec Lid, Dunvegam, Isle of Skye, Scotland, UK) was put into pancreatic duct about 3 cm through a biopsy channel of duodenoscopy (Olympus JF200, Olympus, Tokyo, Japan) using fluoroscopy by the situational pull through method, and we measured pancreatic duct pressure for a few minutes. Subsequently micro transducer catheter was pulled to papilla. SO basal pressure, SO peak pressure and SO frequency were measured. After that, duodenal pressure was gauged as zero reference. Parameters were obtained PD pressure (mmHg), SO basal pressure (mmHg), SO peak pressure (mmHg), SO frequency (per minute) and duodenal pressure (mmHg). Their pressures were determined through the waveforms.

After measurement, a guide wire was replaced using the diagnostic cannula in the CBD. A balloon tipped biliary catheter (Olbert and Maxforce catheter system, Boston Scientific Corporation, USA) was inserted into the biliary orifice of the papilla of Vater along the guide wire and inflated to a maximum pressure of 8 atm and a diameter of 10 mm for one minute.

The CBD stones were extracted using a Dormia basket catheter and a balloon extractor. If the stones were over 10 mm in a diameter, a mechanical lithotriptor (BML-4Q, Olympus, Tokyo, Japan) was used to crush them and removed. Subsequently the CBD was washed by saline through a diagnostic cannula repeatedly. The serum amylase was collected at before EPBD, one, two, three, four, five, six, twelve, eighteen, twenty-four, and forty eight hours after EPBD. Complications were evaluated according to the consensus document published by Cotton, *et al.* (20) and Ueno, *et al* (21).

Two experts endoscopist examined the EPBD, who had more than fifteen years experience.

STUDY DESIGN AND STATISTICAL ANALYSIS

All data are expressed as a mean ± standard deviation (SD). To compare SO basal pressure, SO peak pressure, SO frequency, and PD pressure, Wilcoxon rank-sum test was used. Serum amylase date was subjected to analysis of repeated measure ANOVA. A P-values of <0.05 was considered to be significant.

RESULTS

We summarized about the clinical findings, the

stone characteristics, and the complications of the two groups (Table 1). The average age of the group A was almost twelve years older than that of the group B. There were no significant differences of the mean size and the number of CBD stones between two groups. Four cases (33.3%) and three cases (42.9%) used the endoscopic mechanical lithotripsy (EML) in the group A and B respectively. Two of seven cases were occurred the mild acute pancreatitis (28.6%) in the group B.

Endoscopic manometry data were shown (Table 2). The mean value of SO basal pressure in group A was 9.67±0.67 mmHg, and that in group B was 5.43±0.98 mmHg. The mean value of SO basal pressure in the group B was significantly lower than that in the group A ($p<0.01$) (Figure 1a). The mean value of SO peak pressure of the group A was 114.67± 9.56 mmHg, and that of the group B was 94.00± 5.00 mmHg. The group B was also significantly lower than the group A ($p<0.01$) (Figure 1b). Otherwise the mean value of SO contraction frequency of the group A was 17.92±2.54 per minute, and that of the group B was 18.14±2.61 per minute. No significant difference was found in SO contraction frequency between the group A and B ($p=0.90$) (Figure 1c). The mean value of pancreatic duct pressure of the group A was 17.92±4.03 mmHg, and that of group B was 13.71±3.30 mmHg. The mean value of the pancreatic pressure in the group B was significantly lower than that in the group A ($p<0.05$) (Figure 1d).

The group B included the two cases of the mild pancreatitis. The value of serum amylase after EPBD in group B was higher than that in group A. But it was not significantly different ($p=0.26$) (Figure 2a). On the other hand, the value of serum amylase after EPBD in group B excluding the two cases of mild pancreatitis tended to be lower than that in group A ($p=0.09$) (Figure 2b).

Table 1 Baseline characteristics of the 19 patients with common bile duct stones receiving EPBD

Characteristic	Group A	Group B
Number	12	7
Sex (M/F)	8/4	2/5
Mean age (yr.)	77.0±9.9	63.5±15.5
Bile duct stones		
Number	2.4±1.6	2.3±1.0
Mean size (mm)	9.7±6.5	8.7±4.7
Mechanical lithotripsy	4(33.3%)	3(42.9%)
Gall bladder stones	6(50.0%)	4(57.1%)
Cholecystectomy	3(25.0%)	1(14.2%)
Complications		
Pancreatitis		
Mild	0	2(28.6%)
Moderate	0	0
Severe	0	0
Hemorrhage	0	0
Perforation	0	0

EPBD : Endoscopic Papillary Balloon Dilation, Group A : prophylactic administration with gabexate mesilate (GM) immediately after EPBD, Group B : prophylactic administration with GM before EPBD

Table 2 Comparison of the manometric data between the group A and the group B

	Group A (n=12)	Group B (n=7)
SO basal pressure (mmHg)	9.7±0.7(7-15)	5.4±1.0(4-7)**
SO peak pressure (mmHg)	114.7±9.6(101-131)	94.0±5.0(89-102)**
SO contraction frequency (per min)	17.9±2.5(13-22)	18.1±2.6(15-21)
Pancreatic duct pressure (mmHg)	17.9±4.0(12-25)	13.7±3.3(9-18)*

Group A : prophylactic administration with gabexate mesilate (GM) immediately after EPBD,
Group B : prophylactic administration with GM before EPBD, SO : sphincter of Oddi Values are mean±S.D. (range), **$p<0.01$,*$p<0.05$ compared with Group A

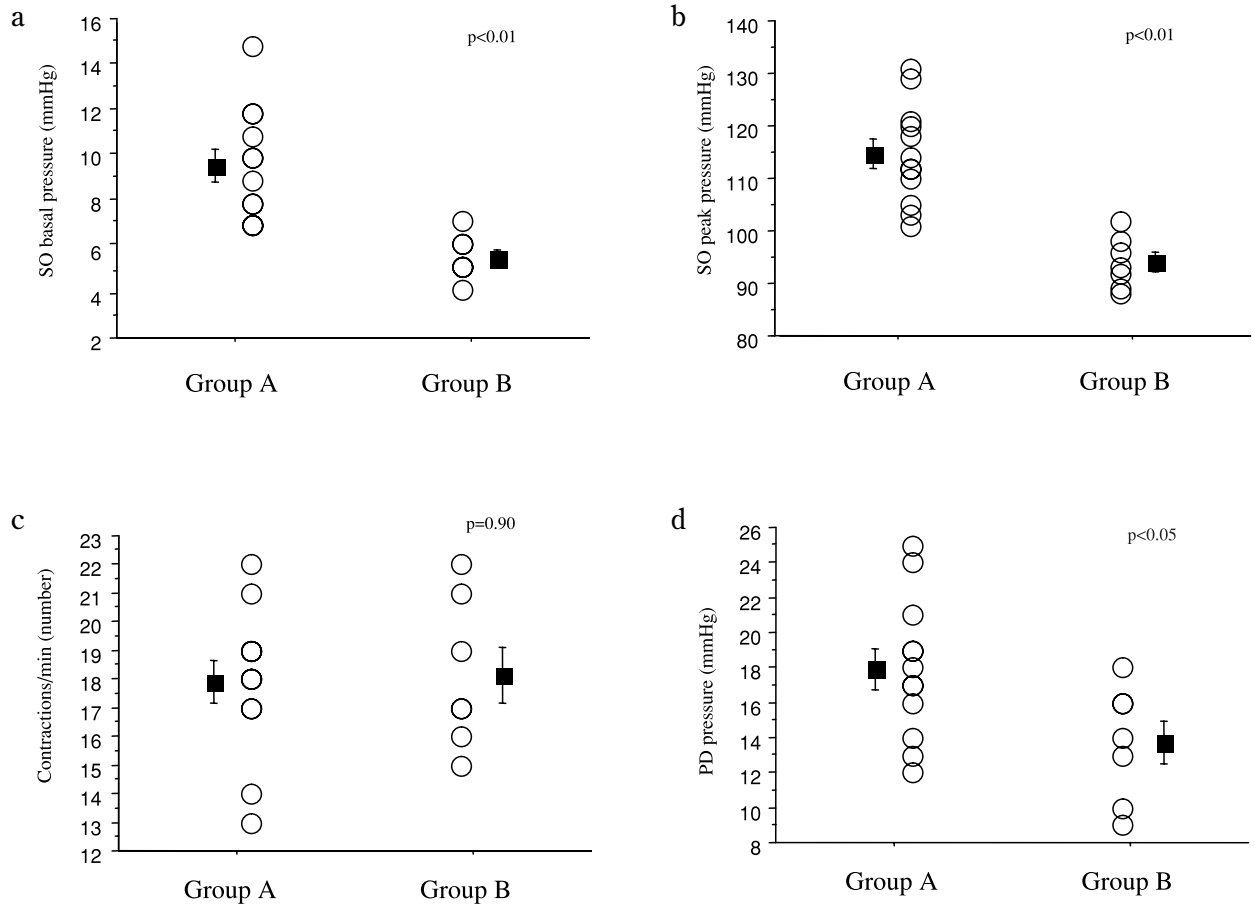

Figure 1. The circle indicated the individual case. And the symbol with ranges showed the mean value ± SD.
a. Comparison of sphincter of Oddi basal pressure of the papilla between the groups A and B before EPBD. The two groups were significantly different ($p<0.05$).
b. Comparison of sphincter of Oddi peak pressure of the papilla between the group A and B before EPBD. The two groups were significantly different ($p<0.01$).
c. Comparison of the sphincter of Oddi contraction frequency of the papilla between the group A and B before EPBD. The two groups were no different ($p=0.90$).
d. Comparison of the PD pressure between the group A and B before EPBD.
The two groups were significantly different ($p<0.05$).

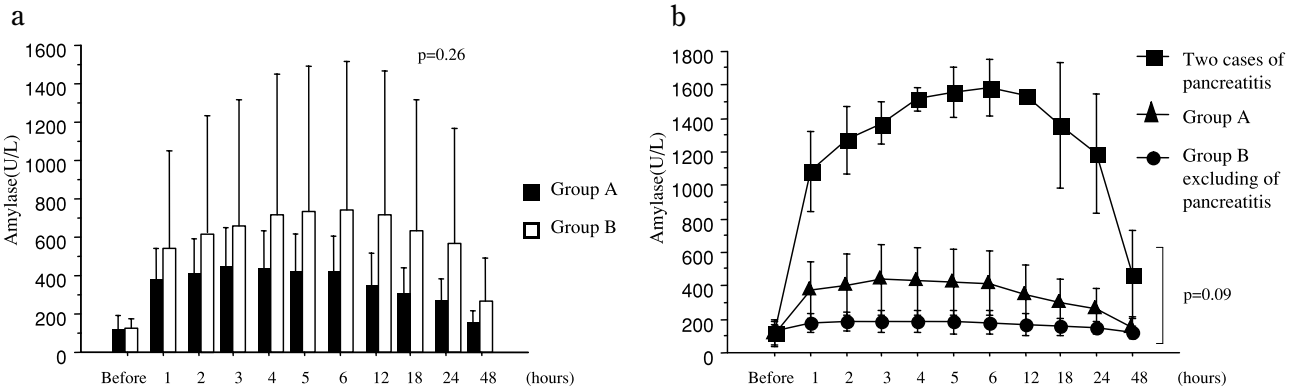

Figure 2. Serum amylase data, which were collected at eleven times.
a. Comparison of the serum amylase between the group A and B. The bar with ranges showed the mean value ± SD. The group A was lower than the group B, but there is no significantly difference statistically ($p=0.26$).
b. Comparison between the group A, the group B excluding the two cases of mild acute pancreatitis, and two cases of acute pancreatitis. The symbol with ranges showed the mean value ± SD. The group A was higher than the group B that excluded the two cases of mild acute pancreatitis. But there is no significantly difference statistically ($p=0.09$).

DISCUSSION

The sublingual nitroglycerin tablet, epinephrine irrigation and isosorbide dinitrate drip infusion relaxed SO function. It makes less traumatic injury for the papilla because of facility of balloon dilation or extraction of CBD stones. And they prevent the obstruction by the edema of papilla. Also the stent placement in the PD after EPBD prevented the obstruction of the papilla forcibly (13-16). Gregg and Carr-Locke reported a rise of the PD pressure at the acute pancreatitis, and it might be caused by a kind of sphincter dysfunction and outflow obstruction (12). The decrease of the flow of the pancreatic juice would result in PD hypertension with pancreatic exocrine stimulation. The activated pancreatic enzymes escaped from the PD into the surrounding parenchyma, and eventually acute pancreatitis. Therefore it is thought that maintenance of the enough flow of the pancreatic juice is the most important point for preventing the acute pancreatitis after EPBD.

GM already has been reported to be effective in the case of DIC, multiple organ failure, and the acute pancreatitis. It can markedly suppress the activity of several proteases, including trypsin, kallikrein, thrombin plasmin, C1 esterase, phospholipase A2, and prostagrandin synthesis. It was suggested that GM prevented the alteration of intracellular transport, the elevation of serum amylase by blocking esterase, and the inflammatory response by the release of acute phase proteins in acute pancreatitis (17, 22).

SO contraction is coordinated by a neural network connecting the jejunum, SO, and gallbladder. The role of neuropeptides and hormones in physiological has not been completely clarified. Di Francesco, *et al*. reported that GM reduced only SO peak pressure and frequency, but had no effect on SO basal pressure. They injected GM 100 mg over 5 minutes, and measured SO pressure immediately. Therefore they suggested that the very rapid response of infusion of GM would have a neuromediated mechanism (18). However our report revealed that GM decreased SO basal and peak pressure by dripping infusion at 2mg/kg/hr. But GM had no effect on SO frequency. It suggested GM loosened SO and reduced the resistance through the sphincter by direct stimulation of the smooth muscles. Similar to our experiment, Okushima, *et al*. reported GM inhibited only SO basal and peak pressure at 20 minutes after dripping infusion of GM at 1-3 mg/kg/h, and SO pressure dose-dependent reduced by GM (23).

Then our report showed that GM had some effect of reducing the PD pressure through the obvious inhibiting of the SO basal and peak pressure. Although the group B was administered GM before EPBD, it included two cases of mild acute pancreatitis. The average age of the group B was almost twelve years younger than that of the group A. The age is known risk factor of acute pancreatitis because the younger age increased the pancreatic exocrine (24). It might be affected by the age. Otherwise the serum amylase value in the group B excluding the two cases with acute pancreatitis tended to be lower than that in the group A. GM might have some effect to reduce the hyperamylasemia, but the effect of GM would not prevent the occurrence of acute pancreatitis completely.

We revealed the change of the serum amylase with administration of GM. The serum amylase of the two cases with mild acute pancreatitis in group B raised 917 and 1253 U/L one hour after EPBD, and they continued to rise at 1462 and 1700 U/L six hours after EPBD separately. The serum amylase of other cases in group B showed 589 U/L at maximum one hour after EPBD and the maximum difference was within 196 U/L from 1 to 6 hours after EPBD in. Even though our data was under administration of GM, it might be useful marker to review the value and the change of serum amylase at twice within six hours, which included one hour after EPBD.

In summary, GM reduced PD pressure through the loosened SO in addition to suppress some proteases, although it could not have enough effect to prevent the acute pancreatitis after EPBD.

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