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The Use of Gabexate Mesylate and Ulinastatin for the Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

Young Wook Yoo*, Sang-Woo Cha†, Anna Kim‡, Seung Yeon Na‡, Young Woo Lee‡, Sae Hee Kim‡, Hyang Ie Lee‡, Yun Jung Lee‡, Hyeon Woong Yang‡, and Sung Hee Jung‡

Gastroenterology and Hepatobiliary Center, Department of Internal Medicine, Cheongju St. Mary's Hospital, Cheongju, †Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, and ‡Division of Gastroenterology, Department of Internal Medicine, Daejeon Eulji University Hospital, Eulji University College of Medicine, Daejeon, Korea

Background/Aims: Acute pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP). Only a few pharmacologic agents have been shown to have potential efficacy for the prophylactic treatment of post-ERCP pancreatitis (PEP). The aim of this study was to determine whether prophylactic gabexate and ulinastatin can decrease the incidence of PEP. **Methods:** From January 2005 to April 2010, 1,679 patients undergoing ERCP treatment were consecutively enrolled in the study. After selective exclusion, a total of 1,480 patients were included in the analysis. The patients were separated into 3 groups according to the prophylactic administration of gabexate (593 patients), ulinastatin (229 patients), or saline solution (658 patients) and analyzed retrospectively. The primary outcome measurements were the incidence of pancreatitis and hyperamylasemia. **Results:** PEP occurred in 21 of the 593 (3.5%) patients who received gabexate, 16 of the 229 (7.0%) patients who received ulinastatin, and 48 of the 658 (7.3%) patients who received a saline solution. The incidence of PEP was significantly different between the gabexate and ulinastatin or saline solution groups ($p<0.05$). **Conclusions:** Gabexate prophylaxis is effective in preventing PEP. However, there is no difference in the beneficial effects of the prophylactic administration of ulinastatin and a saline solution. **(Gut Liver 2012;6:256-261)**

Key Words: Endoscopic retrograde cholangiopancreatography; Pancreatitis; Gabexate; Ulinastatin

INTRODUCTION

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), it is most often clinically mild or moderate in severity but in about 10% of cases it is severe and potentially fatal.[1] Despite improvements in technology and more experience in ERCP, the incidence of post-ERCP pancreatitis (PEP) has not yet decreased significantly. PEP is associated with substantial morbidity and even mortality. Although the pathophysiology of PEP is not completely understood, numerous factors, including hydrostatic injury, obstruction of pancreatic juice outflow, thermal injury from electrocautery current, and chemical or allergic injury, can act independently or in combination to induce PEP.[2]

The pharmacologic agents that have been proposed and tested for prophylaxis of PEP are various, but only a few have been shown to have any proven efficacy. In a recent European Society of Gastrointestinal Endoscopy guideline for prophylaxis of PEP[1] non-steroidal anti-inflammatory drugs are the only drugs with proven efficacy. Glyceryl trinitrate (nitroglycerin), ceftazidime, somatostatin, octreotide, and antiprotease drugs are possibly effective drugs. However, glucocorticoids; drugs reducing pressure on the sphincter of Oddi other than nitroglycerin, such as botulinum toxin, epinephrine, lidocaine, and nifedipine; antioxidant drugs such as allopurinol, n-acetylcysteine, and heparin; and interleukin-10 were proven ineffective.[1]

Antiproteases, which have been clinically used to manage acute pancreatitis, would theoretically reduce pancreatic injury after ERCP because activation of proteolytic enzymes is considered to play an important role in the pathogenesis of PEP.

Correspondence to: Sang-Woo Cha
Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Soonchunhyang University School of Medicine, 59 Daesagwan-ro, Yongsan-gu, Seoul 140-743, Korea
Tel: +82-2-709-9212, Fax: +82-2-709-9696, E-mail: swcha@schmc.ac.kr
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Currently, three antiproteases; gabexate mesylate, ulinastatin, and nafamostat have been evaluated for their prophylactic efficacy against PEP in prospective randomized controlled trials.[2-6] However, most results are controversial, prophylaxis against PEP with these drugs has been carried out using various drug dosages, and no adequate study has been performed to identify the optimal method or dosage of administration of the drugs.

The present study was designed to evaluate retrospectively the efficacy of intravenous gabexate mesylate and ulinastatin in preventing PEP and hyperamylasemia in comparison with control group.

MATERIALS AND METHODS

1. Patients

From January 2005 to April 2010, 1,679 patients underwent ERCP in the gastrointestinal endoscopy unit of Eulji University Hospital (a tertiary referral center) were consecutively enrolled. Exclusion criteria were as follows: age <19 years, previous sphincterotomy, acute pancreatitis before ERCP, and pregnancy. After selective exclusion, a total of 1,480 patients were included in the analysis. Patients were separated into 3 groups according to the prophylactic administration of a continuous intravenous infusion of gabexate mesylate (400 mg, 593 patients, group A), ulinastatin (150,000 units, 229 patients, group B), or saline solution (658 patients, group C), and analyzed retrospectively (Fig. 1). Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board of our hospital.

2. Administration of gabexate mesylate or ulinastatin, and follow-up

Four hundred milligram of gabexate mesylate (Foy; Dong-A Pharmaceutical, Seoul, Korea) or 150,000 units of ulinastatin (Ulistin; Hanlim Pharmacy, Seoul, Korea) was dissolved in 500 mL of 5% dextrose solution and administered by continuous intravenous infusion beginning 30 minutes before ERCP and continuing for 24 hours afterwards. In group C, 500 mL of saline solution was administered by continuous infusion during the same time as control (Fig. 1). Benzodiazepines, anti-spasmodic agents, and non-narcotic analgesics, alone or in combination, were administered routinely before the procedure. Therapy with antibiotics and analgesics was allowed to be continued. Two senior endoscopists directly performed all the procedures using side-viewing endoscopes (JF-240, JF-260V, and TJF-240; Olympus Optical Co., Ltd., Tokyo, Japan). Serum amylase and lipase levels were checked before ERCP, 4 and 24 hours after ERCP, and when clinically indicated. The presence of abdominal pain attributable to the pancreas and the use and type of analgesic therapy at those times were evaluated. The primary outcome measurements were the incidence of pancreatitis and hyperamylasemia.

3. Definitions

The definition of PEP was based on the consensus criteria.[7] It was defined as the following: a newly developed or increased abdominal pain within 24 hours after ERCP requiring analgesic agents, and the elevation of serum amylase and/or lipase level

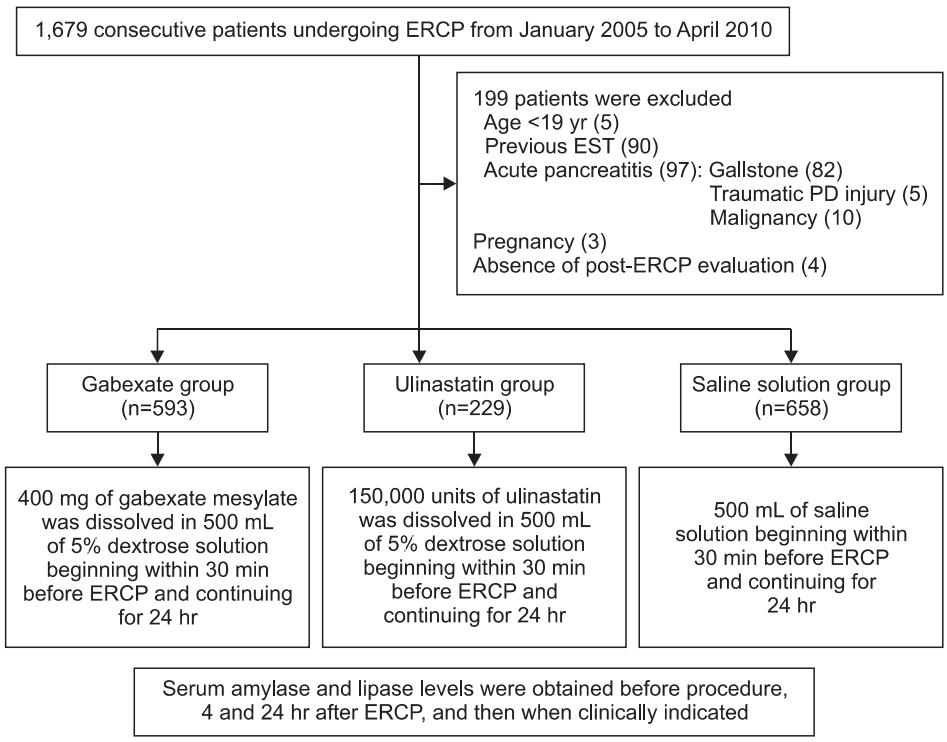

Fig. 1. Study flow diagram.
ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy; PD, pancreatic duct.

at least 3 times the normal upper limit about 24 hours after the procedure. The severity was graded mild when hospitalization lasted 2 to 3 days, moderate when it lasted 4 to 10 days, and severe when it was prolonged for more than 10 days or any of the following complications occurred: hemorrhagic pancreatitis, pancreatic necrosis, pancreatic pseudocyst, or a need for percutaneous drainage or surgery. Hyperamylasemia was defined as elevation of serum amylase levels to more than 3 times the normal upper limit at 4 and/or 24 hours after the ERCP without other symptoms. Visualization of the entire pancreatic duct by contrast injection was regarded as pancreatic injection. Precut sphincterotomy was performed at the periampullary area, and infundibulotomy was not performed. Difficult cannulation, based on the number of attempts on the papilla with a cannulating instrument, was defined as more than 10 attempts occurred, or failure of cannulation after 10 minutes.[8] Failed selective bile duct cannulation was categorized into the "difficult cannulation" group.

4. Statistical analysis

The χ^2 and Fisher exact test were used for comparisons of categorical data. All continuous data values were expressed as means±SD. Differences in variance of the data between the 3 groups were examined by repeated measures analysis of variance and Bonferroni's method was employed for within subjects comparisons. Differences in the mean values were examined by Student's t-test. A $p<0.05$ indicated statistical significance. Statistical calculations were performed with SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 1,679 total patients who were enrolled for the study, 199 were excluded from the final analysis for the following reasons: age <19 years (5 patients), previous sphincterotomy (90 patients), acute pancreatitis before ERCP (97 patients), pregnancy (3 patients), and absence of post-ERCP evaluation (4 patients). The "previous sphincterotomy" group included any patients with a history of a biliary sphincterotomy, biliary stent removal or replacement, or confirmation of biliary clearance after stone extraction.

Ultimately, data from 1,480 patients (gabexate mesylate group, 593; ulinastatin group, 229; control group, 658) were analyzed. The mean age was 65.19±15.23 years, and 691 (46.7%) patients were women. The most common indication for ERCP was choledocholithiasis (59.1%, 874/1,480), followed by cholecystolithiasis (10.9%, 162/1,480), cholangiocarcinoma (9.9%, 146/1,480), and pancreatic cancer (5.2%, 77/1,480). The gabexate mesylate, ulinastatin, and control groups were similar in respect to patient demographics and the common distribution of indications for the procedure (Table 1). Patients were classified as high risk if they had any of the high-risk parameters

Table 1. Baseline Characteristics of Patients in the Gabexate Mesylate, Ulinastatin, and Control Groups

Characteristic	Group A	Group B	Group C	p-value
	Gabexate (n=593)	Ulinastatin (n=229)	Control (n=658)	
Gender				
Male	303 (51.1)	128 (55.9)	358 (54.4)	NS
Female	290 (48.9)	101 (44.1)	300 (45.6)	NS
Age, mean±SD	65.5±15.2	65.6±15.4	64.7±15.2	NS
Main indication for ERCP				
Choledocholithiasis	350 (59.0)	144 (62.9)	380 (57.8)	NS
Cholecystolithiasis	54 (9.1)	27 (11.8)	81 (12.3)	NS
Cholangiocarcinoma	54 (9.1)	18 (7.9)	74 (11.2)	NS
Pancreatic cancer	33 (5.6)	7 (3.1)	37 (5.6)	NS
Miscellaneous bile duct disease	69 (11.6)	24 (10.5)	75 (11.4)	NS
Miscellaneous pancreatic duct disease	33 (5.6)	9 (3.9)	11 (1.7)	NS
High risk group	102 (17.2)	44 (19.2)	106 (16.1)	NS
Age <40 yr	46 (7.8)	25 (10.9)	54 (8.2)	NS
Prior pancreatitis	19 (3.2)	6 (2.6)	9 (1.4)	NS
Suspected SOD	3 (0.5)	0 (0.0)	1 (0.2)	NS
Difficult cannulation	24 (4.0)	15 (6.6)	26 (4.0)	NS
Precut sphincterotomy	10 (1.7)	6 (2.6)	16 (2.4)	NS

Data are presented as mean±SD or number (%).
NS, not significant; ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction.

identified by Freeman and Guda,[9] such as young age, suspected sphincter of Oddi dysfunction, prior pancreatitis, difficult cannulation, or precut sphincterotomy. Of the total 252 high-risk patients, 102 were in the gabexate mesylate group, 44 were in the ulinastatin group, and 106 were in the control group. The incidence of high-risk factors for PEP was similar in the 3 groups (Table 1).

Endoscopic sphincterotomy was performed in about 63.8% (944/1,480) of the therapeutic endoscopic procedures, with no significant differences among the 3 groups. Also similar were the rates of patients with bile duct cannulation failure, precut sphincterotomy, endoscopic sphincterotomy and/or stone extraction, endoscopic papillary balloon dilation (EPBD) and/or stone extraction, stricture dilation, endoscopic retrograde biliary drainage, and endoscopic papillectomy (Table 2). However, EPBD was performed more in the ulinastatin group (19.7%, 45/229) than in the gabexate mesylate group (10.8%, 64/593) and control group (10.7%, 70/658), and this difference was significant (p=0.001).

1. Post-ERCP hyperamylasemia and PEP

The overall incidence of post-ERCP hyperamylasemia was 12.9% (192/1,480). There was no significant difference in the rate of post-ERCP hyperamylasemia between the gabexate mesylate (12.3%, 73/593), ulinastatin (10.9%, 25/229), and control (14.3%, 94/658) groups (p=0.351). PEP was developed in 5.7% (85/1,480) of the patients. There was a significant difference in the rate of PEP between the gabexate mesylate (3.5%, 21/593), ulinastatin (7.0%, 16/229), and control (7.3%, 48/658) groups (p=0.012). Moreover, patients who were given gabexate mesylate (3.5%) had lower rates of PEP than those who were given ulinastatin (7.0%), and this difference was statistically significant (p=0.039). Among the 85 patients who developed pancreatitis, 24 (28.3%) had moderate to severe pancreatitis (3 patients in the gabexate mesylate group, 6 in the ulinastatin group, and 15 in the control group). There was a significant difference in the rate of moderate to severe PEP between the gabexate mesylate (0.5%, 3/593), ulinastatin (2.6%, 6/229), and control(2.3%, 15/658) groups (p=0.020) (Table 3).

2. Side effects

None of the patients experienced any adverse effects related to gabexate mesylate, ulinastatin or saline solution administration, such as shock, itching, rash, nausea, vomiting, or neutro-

Table 2. Therapeutic Procedures for Each Group

Variable	Group A	Group B	Group C	p-value
	Gabexate (n=593)	Ulinastatin (n=229)	Control (n=658)	
Failure of BD cannulation	10 (1.7)	4 (1.7)	20 (3.0)	NS
Precut sphincterotomy	10 (1.7)	6 (2.6)	16 (2.4)	NS
EST	368 (62.1)	156 (68.1)	420 (63.8)	NS
EST with stone extraction	236 (39.8)	107 (46.7)	255 (38.8)	NS
EPBD	64 (10.8)	45 (19.7)	70 (10.7)	0.001
EPBD with stone extraction	54 (9.1)	41 (17.9)	60 (9.1)	<0.001
EPBD with stricture dilatation	10 (1.7)	4 (1.7)	10 (1.5)	NS
Biliary drainage	244 (41.1)	73 (31.9)	272 (41.3)	NS
Endoscopic papillectomy	2 (0.3)	2 (0.9)	1 (0.2)	NS

Data are presented as number (%).
BD, bile duct; NS, not significant; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilatation.

Table 3. Incidence of Post-ERCP Hyperamylasemia and Post-ERCP Pancreatitis in Each Group

Variable	Group A	Group B	Group C	p-value
	Gabexate (n=593)	Ulinastatin (n=229)	Control (n=658)	
Hyperamylasemia	73 (12.3)	25 (10.9)	94 (14.3)	NS
Incidence of post-ERCP pancreatitis	21 (3.5)*,†	16 (7.0)*	48 (7.3)†	0.012
Severity of post-ERCP pancreatitis				
Mild	18 (3.0)	10 (4.4)	33 (5.0)	NS
Moderate to severe	3 (0.5)‡,§	6 (2.6)‡	15 (2.3)§	0.020

Data are presented as number (%).
NS, not significant; ERCP, endoscopic retrograde cholangiopancreatography.
*Group A vs group B, p=0.039; †Group A vs group C, p=0.004; ‡Group A vs group B, p=0.017; §Group A vs group C, p=0.009.

penia.

DISCUSSION

ERCP and sphincterotomy are essential procedures for managing pancreaticobiliary disease. Among the complications of ERCP, acute pancreatitis is the most frequent and troublesome. The pathogenesis of PEP is not well understood but is most likely multifactorial. Hypothesized mechanisms of pancreatic injury include mechanical, chemical, hydrostatic, thermal, enzymatic, microbiologic, allergic, immunologic reactions, etc. On the basis of the hypothesis, various attempts have been made to prevent PEP, such as change of technique, patient selection, pancreatic stenting, and pharmacologic prophylaxis.[10]

Many pharmacologic agents of different types have been used to prevent PEP on the assumption that they may pharmacologically inhibit one or more of the aforementioned factors associated with pancreatic damage. Irrespective of the etiology of acute pancreatitis, the activation of proteolytic enzymes, starting with trypsinogen activation to trypsin in pancreatic acinar cells, has been considered to play an initial role in the pathogenesis of pancreatitis. Trypsin would subsequently trigger the activation of other enzymes and the inflammatory cascade. Antiproteases, which have been used to manage acute pancreatitis in routine clinical settings in some countries,[11] may be theoretically useful for preventing PEP. Prevention of PEP with antiproteases, gabexate, or ulinastatin, has been evaluated in several studies. Some studies clearly demonstrated that gabexate mesylate or ulinastatin is effective in reducing the incidence of PEP,[2,4,8,12,13] other studies did not find any benefit in administrating either drug.[3,5,12] Compared with gabexate mesylate, ulinastatin has a stronger inhibitory effect on pancreatic enzymes in various experimental models of pancreatitis.[14] To date, however, very a few reports comparing the efficacy of gabexate mesylate and ulinastatin with regard to the prevention of PEP have been published. Two Japanese clinical trials compared gabexate mesylate with ulinastatin administered before and after ERCP, and the rates of PEP were not significantly different.[13,15]

In our study, in a consecutive series of hospitalized patients who underwent ERCP, we compared the effects of a 24-hour continuous intravenous drip infusion of either 400 mg of gabexate mesylate or 150,000 units of ulinastatin, beginning 30 minutes before the ERCP. We found that gabexate mesylate prophylaxis before and after ERCP was effective in preventing PEP. However, prophylactic administration of ulinastatin did not show a beneficial efficacy to prevent PEP. Recent systemic review reported ulinastatin shows to be of value on preventing PEP and hyperamylasemia for patients in average risk, when given intravenously at a dose of not less than 150,000 unit, just before ERCP.[16] In our study, we designed to 150,000 unit of ulinastatin infusion duration for 24 hours start from 30 minutes before ERCP. Considering duration of infusion and difference of infusion dose intensity, it could make different result from other previous studies.

In general, because of its short half-life, gabexate should be administered continuously for a long period of time (greater than 12 hours) and at a relatively high dose (greater than 500 mg to 1 g) in order to prevent pancreatitis.[2,8,17] In the present study, we used a relatively low dose of gabexate mesylate (400 mg) compared with the previous studies (500 mg or 1 g). In Korea, the cost of 400 mg of gabexate mesylate is about US $18, whereas 150,000 units of ulinastatin is US $44. And the cost of continuous infusion of 0.75 mg and 3 mg of somatostatin, another widely evaluated and possibly effective drug, is about US $40 and US $109, respectively. Thus, gabexate mesylate is more cost effective than either alternative drug. The important results of the present study show that a 24-hour infusion of 400 mg of gabexate mesylate at a relatively lower dose than in previous studies significantly reduced the incidence of PEP.

The increasing risk of pancreatitis after EPBD remains a controversial but serious issue. In an American study,[18] the incidence of pancreatitis was unacceptably high in an EPBD group (15.4%, 18/117), and 2 of 6 patients with severe pancreatitis died. This unfortunate result is in striking contrast to the results of an uncontrolled study and a randomized controlled study; no fatal pancreatitis was observed after EPBD in a total of more than 600 patients reported.[19,20] In our current study, although EPBD is not associated with a risk for PEP (odds ratio, 0.69; 95% confidence interval, 0.09 to 5.36; p=0.722) on univariated analysis, EPBD was performed significantly more in the ulinastatin group (19.7%, 45/229) than in the gabexate mesylate group (10.8%, 64/593) and control group (10.7%, 70/658). This difference may have an effect on the incidence of PEP.

The current study has some limitations. The 3 groups were not randomized, the number of patients with ulinastatin prophylaxis was relatively small compared with other groups, and the analysis was retrospective. In our center, we had changed strategy to premedication for prophylaxis of PEP. It was gabexate mesylate in January 2005 to December 2006, no prophylactic medication in January 2007 to August 2009, and ulinastatin in September 2009 to April 2010. So variation on number of groups is a reflection of changes on number of patients at our center. The study was done in a single large tertiary care center. Most patients needed therapeutic intervention, including endoscopic sphincterotomy or EPBD, and were admitted via the emergency department because of acute cholangitis or severe abdominal pain. Thus, we performed ERCP on an inpatient basis, and continuous intravenous infusion of gabexate mesylate or ulinastatin could be started before the procedure and continued 24 hours thereafter. Thus, it may be impractical to use gabexate mesylate or ulinastatin during outpatient procedures in elective cases.

In conclusion, 24-hour infusion of 400 mg of gabexate mesylate at a relatively low dose significantly reduced the in-

cidence of PEP. However, prophylactic administration of ulinastatin, compared with gabexate mesylate and control group, did not show a beneficial influence on the incidence of PEP. Further prospective randomized large multicenter studies are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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