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Comparison between ulinastatin and gabexate mesylate for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a prospective, randomized trial

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Background. It has been reported that the administration of ulinastatin, gabexate mesylate, or somatostatin may be effective in the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. However, few randomized trials of ulinastatin and gabexate mesylate for the prevention of post-ERCP pancreatitis have been reported. The aim of this study was to compare the efficacy of ulinastatin and gabexate mesylate for the prevention of post-ERCP pancreatitis. ***Methods.*** Sixty-eight patients who underwent diagnostic ERCP at our hospital were divided at random by computer-generated randomization into an ulinastatin group (n = 34) and a gabexate group (n = 34). Each patient received a continuous intravenous infusion of ulinastatin (150 000 units) or gabexate mesylate (600 mg), beginning 60–90 min before the ERCP and continuing until 22 h after the ERCP. The primary endpoint was the incidence of post-ERCP pancreatitis, and the secondary endpoints were the incidences of hyperenzymemia and pain. ***Results.*** The overall incidence of post-ERCP pancreatitis was 2.9% (two patients), comprising one patient in the ulinastatin group and one patient in the gabexate group (2.9% vs 2.9%, respectively). Neither of these two patients developed severe pancreatitis. There were no significant differences in the serum levels of pancreatic enzymes or in the levels of pain between the two groups. ***Conclusions.*** There was no clinical difference between the effect of preventive administration of ulinastatin and that of gabexate mesylate on the incidence of post-ERCP pancreatitis. Ulinastatin may be equivalent in efficacy to gabexate for reducing the incidence of post-ERCP pancreatitis.

Key words: post-endoscopic retrograde cholangiopancreatography pancreatitis, ulinastatin, gabexate mesylate, endoscopic retrograde cholangiopancreatography, pancreatitis

Introduction

Gabexate mesylate, known to relax the sphincter of Oddi, has been reported to be effective in the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, i.e., pancreatitis secondary to ERCP.[1–6] Moreover, several articles published recently have reported the usefulness of ulinastatin for the prevention of post-ERCP pancreatitis.[7–9] A metaanalysis of studies related to the prevention of post-ERCP pancreatitis has suggested that administration of gabexate mesylate or somatostatin to all patients after ERCP is not economically justifiable and that it would be advisable to limit the use of these drugs to high-risk patients. However, post-ERCP treatment with these drugs has been carried out using various methods, and no adequate study has been performed to identify the optimal method or dose of administration of the drugs. It has been suggested that the serum amylase level measured 22–24 h after ERCP may serve as a useful predictor of post-ERCP pancreatitis.[10] The present study was undertaken to comparatively assess the efficacy of ulinastatin and gabexate mesylate, both administered by intravenous drip infusion for 22 h after the ERCP, with regard to the prevention of post-ERCP pancreatitis.

Subjects and methods

Patients

Between January 2002 and August 2003, a cohort of 303 consecutive patients was admitted for ERCP to the

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Department of Gastroenterology at Fukuoka University Chikushi Hospital. Among these patients, 134 who underwent diagnostic ERCP were considered for this study, because these patients were undergoing the examination for the first time. Of these 134 patients, 64 did not meet the inclusion criteria: declined to participate in the study (7 patients), active acute pancreatitis (5 patients), and choledocholithiasis (52 patients). Written informed consent was obtained from all of the remaining patients prior to their participation in the study. The study was approved by the ethics committee at our hospital.

Study design

We conducted a prospective randomized trial at our hospital. A thorough clinical history was obtained from all the participants, and the reason for the endoscopic examination was clearly recorded. All the patients undergoing the ERCP were hospitalized. One endoscopist, with experience in performing over 200 ERCPs per year for a period of more than 15 years, performed all of the ERCPs. Patients who fulfilled the inclusion criteria and agreed to participate in the study were allocated randomly to an ulinastatin group (35 patients) or a gabexate group (35 patients) by computer-generated randomization. In 1 patient each from the ulinastatin group and the gabexate group, observation of the duodenal papilla was not possible because of previous partial gastrectomy, and therefore these patients were excluded from the analysis. Finally, 34 patients in each of the ulinastatin group and the gabexate group were included for the analysis.

In the ulinastatin group, 2500 ml of 5% glucose solution with electrolytes, containing 150 000 units of ulinastatin (Miracrid, Mochida Pharmaceutical, Tokyo, Japan), was administered by continuous intravenous infusion, beginning 60 to 90 min before the endoscopy; this was continued until 22 h after the procedure. In the gabexate group, 2500 ml of 5% glucose solution with electrolytes, containing 600 mg of gabexate mesylate (FOY; Ono Pharmaceutical, Tokyo, Japan), was administered by continuous intravenous infusion, beginning 60 to 90 min before the endoscopy session; this was continued until 22 h afterward. Diazepam, and a spasmolytic agent such as hyoscine-N-butylbromide, and glucagon (Glucagon G Novo; Novo Nordisk Pharma, Tokyo, Japan) were administered routinely before the procedure. Therapy with antibiotics, analgesics, and sedatives was allowed to continue.

All the patients were hospitalized for at least 3 days after the ERCP and fasted for at least 22 h after the ERCP. The body temperature and white blood cell count, and the serum levels of C-reactive protein and amylase, were measured before and 3, 18, 42, and 66 h after the ERCP in all the patients, and the interleukin-6 (IL-6) levels were also measured at the same time-points in some patients. The serum levels of lipase and elastase 1 were measured before and 3, 18, and 42 h after the ERCP in all the patients. Abdominal ultrasound (US) and computed tomography (CT) were performed as needed. Each patient was checked for post-ERCP pain, hyperenzymemia, and pancreatitis. The primary endpoint was the incidence of pancreatitis after ERCP, and the secondary endpoints were the incidences of hyperenzymemia and pain.

Definitions

Hyperenzymemia was defined as elevation of serum amylase, lipase, and/or elastase 1 levels to more than three times the upper limit of normal at 3 and/or 18 h after the ERCP. Pancreatic pain was defined as persistent pain in the epigastrium and periumbilical region, with or without radiation to the back. Post-ERCP pancreatitis was defined as abdominal pain persisting for at least 24 h after the ERCP and associated with the elevation of serum amylase, lipase, and/or elastase 1 levels to at least three times the upper limit of normal at 18 h after the ERCP. Pancreatitis was graded according to the modified 1991 Consensus Guidelines,[11] as follows: mild, requiring fasting and treatment for 3 days or less; moderate, requiring fasting and treatment for 4–10 days; severe, requiring fasting and treatment for more than 10 days, plus intensive care or surgical intervention.

Statistical analysis

The χ^2 and Fischer's exact tests were used for comparisons of categorical data. All continuous data values were expressed as means ± SE. Differences in variance of the data between the two groups was examined by repeated measures ANOVA and Bonferroni's method was employed for within subjects comparisons. Differences in the mean values were examined by Student's *t*-test. The significance level was set at a *P* value of less than 5% and the trend toward significance at a value of 5% to 10%.

SPSS 11.5J for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical processing.

Results

Baseline characteristics of the patients

The two treatment groups were similar with regard to sex, age, body mass index (weight in kilograms divided by square of the height in meters) and indications for endoscopy (Table 1).

Table 1. Characteristics of the patients and indications for ERCP

Characteristics	Ulinastatin group ($n = 34$)	Gabexate group ($n = 34$)	P value
Sex (male/female)	25/9	22/12	0.60
Age, years (mean ± SE)	66 ± 2	61 ± 2	0.12
Body mass index	23 ± 0.6	22 ± 0.6	0.27
Main indication for ERCP			0.51
Cholecystolithiasis	2	2	
Miscellaneous biliary disease	6	3	
Chronic pancreatitis	9	14	
Cystic pancreatic tumor	9	9	
Pancreatic cancer	6	6	
Miscellaneous pancreatic disease	2	0	

Table 2. Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis, abdominal pain, and hyperenzymemia

	Ulinastatin group ($n = 34$)	Gabexate group ($n = 34$)	P value
Pancreatitis:	1 (2.9%)	1 (2.9%)	
Mild	1	1	
Moderate or severe	0	0	
Abdominal pain	4 (11.8%)	7 (20.6%)	0.51
Hyperamylasemia	11 (32.4%)	7 (20.6%)	0.41
Hyperlipasemia	25 (73.5%)	20 (58.8%)	0.31
Hyperelastasemia	8 (23.5%)	6 (17.6%)	0.77

Acute pancreatitis

The overall incidence of acute pancreatitis was 2.9% (two patients; one each in the ulinastatin group and the gabexate group). The acute pancreatitis was clinically mild and edematous in both patients, as assessed by abdominal US and/or CT. Thus, both ulinastatin and gabexate were considered to be equally effective in the prevention of post-ERCP pancreatitis (Table 2).

Pain

Of the 68 patients, 11 (16.2%) complained of pancreatic pain after the ERCP (Table 2). The pain in all the patients began within the first 3 h after the ERCP, and ameliorated within 18 h after the ERCP, with the exception of 2 of the 11 patients. These 2 patients developed post-ERCP pancreatitis. There were no significant differences in the pancreatic pain between the two groups ($P = 0.51$; Table 2). The serum levels of amylase, lipase, and elastase 1 at 3 and 18 h after the ERCP in the 9 patients with pain and without pancreatitis were 504 ± 73 IU/l, 707 ± 170 U/l, and 744 ± 117 U/l; and 378 ± 52 IU/l, 269 ± 66 U/l, and 652 ± 88 U/l, respectively. Accordingly, the serum levels of the three pancreatic enzymes in these 9 patients were elevated at 3 h after the ERCP, while the serum levels of all three enzymes were lower at 18 h after the ERCP than they had been at 3 h.

Hyperenzymemia

Before the ERCP, 42 patients (62%; 22 in the ulinastatin group and 20 in the gabexate group; $P = 0.80$) had serum amylase, lipase, and elastase 1 levels within the upper limit of the normal range, while 26 patients (38%; 12 in the ulinastatin group and 14 in the gabexate group) had elevated basal serum enzyme levels. There was no difference in the variance of serum levels of amylase, lipase, and elastase 1 between the two groups ($P = 0.83$; $P = 0.73$; and $P = 0.55$, respectively). There were no significant differences in the serum levels of the three pancreatic enzymes between the two groups, either before or after the ERCP (Table 3). The extent of elevation of the serum levels of amylase, lipase, and elastase 1 after the ERCP also did not differ significantly between the two groups (Table 2).

Inflammation markers

Before the ERCP, body temperature, white blood cell count, serum level of C-reactive protein, and/or the

Table 3. Serum levels of amylase, lipase, and elastase 1

		Ulinastatin group ($n = 34$)	Gabexate group ($n = 34$)	P value
Amylase (IU/l)	Before	158 ± 22	118 ± 11	0.11
	3 h	410 ± 64	380 ± 69	0.75
	18 h	397 ± 70	329 ± 81	0.53
	42 h	249 ± 29	207 ± 32	0.19
	66 h	119 ± 25	178 ± 16	0.40
Lipase (U/l)	Before	113 ± 40	99 ± 35	0.79
	3 h	647 ± 132	639 ± 171	0.97
	18 h	347 ± 69	342 ± 130	0.97
	42 h	265 ± 70	132 ± 24	0.08
Elastase 1 (U/l)	Before	737 ± 299	463 ± 120	0.40
	3 h	896 ± 154	793 ± 157	0.64
	18 h	861 ± 143	780 ± 212	0.75
	42 h	911 ± 155	624 ± 111	0.14

Table 4. Body temperature, white blood cell count of venous blood, and serum levels of C-reactive protein and interleukin 6

		n	Ulinastatin group	n	Gabexate group	P value
BT (°C)	Before	34	36.3 ± 0.1	34	36.3 ± 0.1	0.98
	3 h	34	36.3 ± 0.1	34	36.5 ± 0.1	0.24
	18 h	34	36.3 ± 0.1	34	36.4 ± 0.1	0.55
	42 h	34	36.4 ± 0.1	34	36.5 ± 0.1	0.11
	66 h	34	36.4 ± 0.1	34	36.5 ± 0.1	0.32
WBC (/mm^3)	Before	34	5564 ± 252	34	6012 ± 354	0.31
	3 h	34	7056 ± 429	34	7442 ± 493	0.56
	18 h	34	5697 ± 341	34	5930 ± 249	0.58
	42 h	34	5476 ± 249	34	6121 ± 411	0.19
	66 h	34	5370 ± 323	34	6088 ± 410	0.18
CRP (mg/dl)	Before	34	0.3 ± 0.1	34	0.7 ± 0.3	0.38
	3 h	34	0.2 ± 0.05	34	0.52 ± 0.24	0.21
	18 h	34	0.51 ± 0.21	34	0.47 ± 0.1	0.80
	42 h	34	0.65 ± 0.21	34	0.49 ± 0.12	0.76
	66 h	34	0.65 ± 0.21	34	0.62 ± 0.23	0.18
IL-6 (pg/ml)	Before	11	4.8 ± 0.9	14	3.0 ± 0.7	0.14
	3 h	11	3.6 ± 0.5	14	9.4 ± 4.0	0.12
	18 h	11	10.5 ± 5.3	14	6.4 ± 2.0	0.52
	42 h	11	10.1 ± 3.0	14	8.4 ± 2.5	0.67
	66 h	11	3.9 ± 0.7	14	8.5 ± 2.6	0.14

BT, Body temperature; WBC, white blood cell count of venous blood; CRP, serum levels of C-reactive protein; IL-6, interleukin 6

serum level of IL-6 were within the normal range in 36 patients (53%; 22 in the ulinastatin group and 14 in the gabexate group; $P < 0.09$) and abnormal in 32 patients (47%; 12 in the ulinastatin group and 20 in the gabexate group). There was no difference in the variance of body temperature, white blood cell count, or the serum levels of either C-reactive protein or IL-6 between the two groups ($P = 0.71$; $P = 0.22$; $P = 0.27$; and $P = 0.27$, respectively). There were no significant differences in the values of these three inflammation markers between the two groups, either before or after the ERCP (Table 4).

Side effects

None of the patients suffered any adverse effects related to ulinastatin or gabexate mesylate administration.

Discussion

Pancreatitis still remains the most frequent and potentially fatal complication of ERCP.[12,13] The activation of trypsinogen to trypsin in the acinar cells of the pancreas seems to play an important role in the pathogenesis of

pancreatitis.[14] Ulinastatin and gabexate are known to be potent inhibitors of trypsin and neutrophil elastase.[15,16] It was, therefore, expected that synthetic protease inhibitors such as ulinastatin and gabexate would perhaps be useful in the prevention of post-ERCP pancreatitis. Several randomized trials of these inhibitors have been published recently (Table 5).[3,5–8,17–20] To date, however, very few reports comparing the efficacy of ulinastatin and gabexate mesylate with regard to the prevention of post-ERCP pancreatitis have been published.[8,9] Meanwhile, Messmann et al.[21] reported the following in relation to the development of post-ERCP pancreatitis: (1) post-ERCP pancreatitis developed about 3–7 h (mean, 4.5 h) after ERCP; (2) the amylase and lipase levels reached their peaks 4–12 h after ERCP; (3) the IL-6 level reached its peak 24–48 h after ERCP; and (4) the serum C-reactive protein level reached its peak 72 h after ERCP. According to Testoni and Bagnolo,[10] post-ERCP pancreatitis was present only in those patients who complained of pain and showed an elevation of serum amylase level to more than five times the upper limit of normal, 24 h after ERCP. Tsujino et al.[7] reported that the administration of ulinastatin immediately before ERCP was useful in preventing post-ERCP pancreatitis, but that the half-life of ulinastatin in vivo was too short (35 min), like that of gabexate (55 s). Their finding suggests the necessity of prolonged infusion of these drugs to achieve the goal of preventing post-ERCP pancreatitis. In the current study, in a consecutive series of hospitalized patients who underwent diagnostic ERCP, we compared the effects of a 22-h continuous intravenous drip infusion of either ulinastatin 150 000 U or gabexate 600 mg (equivalent in potency to 150 000 U of ulinastatin for the treatment of pancreatitis), beginning 60 to 90 min before the ERCP,[22] and found no significant difference in the incidence of post-ERCP pancreatitis, pancreatic pain, or hyperenzymemia between the ulinastatin group and the gabexate group. Furthermore, in the present study, in the 2 of the 11 patients who complained of abdominal pain after the ERCP and who developed post-ERCP pancreatitis, the severity of the pancreatitis was rated as mild according to Cotton's grading system.[11] The serum levels of the three pancreatic enzymes in the remaining 9 patients who complained of abdominal pain after the ERCP were elevated at 3 h after the ERCP; however, the serum levels of all three enzymes were lower at 18 h after the ERCP than they had been at 3 h. Moreover, the abdominal pain in these 9 patients ameliorated within 18 h after the ERCP. It has been reported that, in an experimental model of pancreatic duct occlusion, a progressive rise in serum amylase activity in the 6 h after ductal obstruction was associated with the continued synthesis of digestive enzymes, and it was noted that the serum pancreatic enzyme peak within the first 4 h after ERCP might be the consequence of temporary obstruc-

Table 5. Randomized trials for the prevention of post-ERCP pancreatitis

Study	Drug	*n*	Incidence of pancreatitis (%)	*P* value
Cavallini[3]	Gabexate 1 g over 12 h	208	2	0.03
	Placebo	210	8	
Masci[5]	Gabexate 0.5 g over 6.5 h	214	1.4	NS
	Gabexate 1 g over 13 h	210	2.3	
Xing[6]	Gabexate 0.3 g over 4 h	98	3.1	0.04
	Placebo	95	10.5	
Fujishiro[8]	Gabexate 0.9 g over 13 h	46	4.3	NS
	Ulinastatin 450 000 units for a short term	46	6.5	
	Ulinastatin 150 000 units for a short term	47	8.5	
Tsujino[7]	Ulinastatin 150 000 units for 10 min	204	2.9	0.04
	Placebo	202	7.4	
Andriulli[17]	Somatostatin 750 μg for 6.5 h	351	6.3	NS
	Gabexate 0.5 g for 6.5 h	381	5.8	
	Placebo	395	4.8	
Poon[20]	Somatostatin 250 μg by IVB	135	4.4	0.01
	Placebo	135	13.3	
Deviere[18]	Interleukin-10 4 μg/kg by IV	48	10.4	0.04
	Interleukin-10 20 μg/kg by IV	44	6.8	
	Placebo	45	24.4	
Murray[19]	Diclofenac 100 mg by suppository	110	6.4	<0.05
	Placebo	110	15.5	
Our result	Gabexate 0.6 g over 23 h	34	2.9	NS
	Ulinastatin 150 000 units over 23 h	34	2.9	

NS, not significant; IVB, intravenous bolus injection; IV, intravenous injection

tion of the main pancreatic duct.[5,23] Therefore, it was supposed that the abdominal pain without pancreatitis observed in our study was caused by a temporary elevation of pancreatic duct pressure due to the ERCP.

Ulinastatin is known to suppress the formation of IL-6 and tumor necrosis factor-α (TNF-α), the serum levels of which have been reported to be related to the severity of pancreatitis.[21] In the present study, gabexate was administered at a dose level equivalent in potency to that of ulinastatin, and no significant difference was noted in the serum IL-6 levels (measured serially after ERCP) between the ulinastatin group and the gabexate group.[7,22] The other markers of inflammation (body temperature, white blood cell count, and the serum levels of both C-reactive protein and the pancreatic enzymes) also showed no significant differences between the two groups.

In the present study, there was no clinical difference between the preventive administration of ulinastatin and that of gabexate in relation to post-ERCP pancreatitis. The incidence of post-ERCP pancreatitis varies depending upon the definition of pancreatitis, the population studied, the indications for the procedure, and the intervention performed. The incidence of post-ERCP pancreatitis in the present study was approximately the same as the incidences reported in recent prospective studies in which the definition of pancreatitis and the study population were similar to those in the current study; it was reported that the incidence of post-ERCP pancreatitis was significantly lower in gabexate groups than in placebo groups, and the incidence was also significantly lower in ulinastatin groups than in placebo groups (Table 5). Accordingly, ulinastatin may be equivalent in efficacy to gabexate for reducing the incidence of post-ERCP pancreatitis.

The present study incorporated no control group. As is evident from other studies, post-ERCP pancreatitis is potentially severe and can follow a fatal course. It is, therefore, difficult, from an ethical point of view in Japan, to expect understanding or to obtain approval for participation as a control in studies related to post-ERCP pancreatitis.[8] For this reason, we compared the prophylactic efficacy of ulinastatin and gabexate in this study without incorporating any control group.[8]

Among all the patients undergoing ERCP, multicenter prospective studies have identified various risk factors for post-ERCP pancreatitis, including young age,[24–26] female sex,[27] suspected dysfunction of the sphincter of Oddi,[24,27] previous history of post-ERCP pancreatitis,[27] difficulty in intubation,[24,27] therapeutic ERCP,[8] precut endoscopic sphincterotomy,[24,26,27] pancreatic sphincterotomy,[27] and pancreatography.[24,27] As pointed out by Tsujino et al.,[7] it may be cost-effective to confine prophylactic ulinastatin therapy to patients with a high risk of post-ERCP pancreatitis.

In conclusion, the present randomized trial of ulinastatin and gabexate mesylate revealed that a continuous intravenous infusion of ulinastatin over a period of about 23 h prior to ERCP was comparable to that of gabexate in efficacy, in terms of the prevention of post-ERCP pancreatitis. However, it would be desirable in the future to conduct further studies to determine the optimal dose and timing of the administration of ulinastatin and gabexate for the prevention of post-ERCP pancreatitis using a larger patient sample, including patients undergoing therapeutic ERCP.

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