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Clinical trial of gabexate in the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

The objective of the present study was to determine the efficacy of prophylactic administration of gabexate for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, hyperamylasemia and pancreatic pain. Patients scheduled for ERCP were randomized into two groups in a double-blind manner: the patients in the gabexate group were treated with continuous intravenous infusion of 300 mg gabexate dissolved in 500 mL Ringer's solution at 111 mL/h, starting 30 min before the endoscopic maneuvers and continuing up to 4 h after them; placebo group patients were treated only with Ringer's solution also starting 30 min before the endoscopic maneuvers and continuing up to 4 h. Data for 193 patients were analyzed. The incidence of post-ERCP pancreatitis was 3 patients (3.1%) in the gabexate group and 10 (10.5%) in the placebo group (P = 0.040). The incidence of hyperamylasemia was 33 patients (33.7%) in the gabexate group and 42 (43.7%) in the placebo group (P = 0.133). The incidence of pancreatic pain was 15 patients (15.3%) in the gabexate group and 28 (29.5%) in the placebo group (P = 0.018). The results suggest that a 4.5-h infusion of gabexate (for a total of 300 mg) could prevent post-ERCP pancreatitis and pancreatic pain.

Key words
- Gabexate
- Endoscopic retrograde cholangiopancreatography
- Post-ERCP pancreatitis
- Prevention of pancreatitis
- Hyperamylasemia

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has been used in clinical practice for more than 30 years. A common complication associated with ERCP is acute pancreatitis. Data from recent prospective studies suggest that the frequency of clinical post-ERCP pancreatitis may range from 1 to 24.4% (1,2). The occurrence of post-ERCP pancreatitis is always difficult to predict. A wide range of pharmacological agents have been tested in experimental and clinical trials for the prophylaxis of post-ERCP pancreatitis, such as somatostatin, octreotide and gabexate. A meta-analysis conducted by Andriulli et al. (3) showed that only somatostatin and gabexate consistently presented a moderate beneficial effect. The disadvantage of both drugs is the need for a continuous 12-h intravenous infusion and hence overnight hospitalization. This increases the

cost of the procedure and makes it prohibitive for routine use. However, a multicenter study by Masci et al. (4) has demonstrated that a 6.5-h infusion of gabexate (total: 0.5 g) was as effective as a 13-h infusion (total: 1 g). Serum amylase and lipase values over time, peak levels of the two enzymes, pancreatic pain, and need for analgesics did not differ significantly between the two groups. For a more cost-effective procedure, the present prospective, randomized, double-blind, placebo-controlled study was designed to test the role of a 4.5-h infusion of gabexate (total: 0.3 g) in the prevention of post-ERCP pancreatitis, hyperamylasemia and pancreatic pain.

Material and Methods

Patients

This double-blind, randomized, placebo-controlled clinical trial was conducted at Renji Hospital, Shanghai Second Medical University, between September 2003 and May 2005. The two participating endoscopists were highly trained and had been performing ERCPs for more than 5 years. Moreover, each one had previously performed at least 1000 procedures. The study population consisted of suitably recruited patients aged 18 years or older scheduled to undergo ERCP and, when indicated, endoscopic sphincterotomy. Exclusion criteria were: 1) pregnancy; 2) previous sphincterotomy or therapeutic ERCP; 3) acute myocardial infarction within three months before the study; 4) acute pancreatitis or hyperamylasemia at the baseline blood test; 5) chronic pancreatitis, and 6) history of allergic reaction to gabexate. Informed consent was obtained from all patients who participated in the study, which was approved by the Hospital Ethics Committee.

Study design

Patients were randomly assigned to the gabexate and placebo groups using opaque sealed envelopes according to a computer-generated randomized set of numbers. Randomization and administration of gabexate or placebo were carried out by personnel who were not involved in the endoscopic procedure or the critical care of the patient. Nurses who administered sedation and monitored the vital signs of the patients did not know to which group patients had been assigned. The gabexate group was treated with a continuous intravenous infusion of 300 mg gabexate (Jinyuan Pharma Co. Ltd., Changzhou, China) dissolved in 500 mL Ringer's solution, starting 30 min before the endoscopic maneuvers and continuing up to 4 h after it. The placebo group patients were treated only with Ringer's solution also starting 30 min before the endoscopic maneuvers and continuing up to 4 h. The total infusion time of both groups was 4.5 h. The infusion rate was 111 mL/min. Therapy with antibiotics, analgesics and sedatives was given as required. At the end of each maneuver, the endoscopist recorded procedural details of the maneuvers performed, particularly filling of the biliary and/or pancreatic ducts and their morphological characteristics (namely strictured or normal, with delayed or normal emptying), number of cannulations, number of pancreatic duct injections, whether a needle-knife sphincterotomy was performed, diameter of the bile duct, and the presence of choledocholithiasis. Serum amylase levels were measured before and 4 and 24 h after ERCP. The presence of abdominal pain and other symptoms such as vomiting was also recorded at the same times.

Diagnostic criteria

Following established criteria (5,6), the incidence of post-ERCP pancreatitis was defined as new or worsened abdominal pain for more than 24 h after endoscopy with a more than 5-fold increase in serum amylase level (4 h) or a 3-fold increase (24 h) above

the upper normal limit. The incidence of hyperamylasemia was defined as an elevation in serum amylase levels more than two times the upper normal limit within 4 or 24 h, and the incidence of pancreatic pain was defined as new or worsened abdominal pain persisting for less than 24 h with or without an elevation in serum amylase levels.

Statistical analysis

Data were analyzed statistically by the chi-square test (or Fisher's exact test when appropriate) and Student *t*-test, with the level of significance set at $P < 0.05$.

Results

A total of 200 patients entered the study; 100 patients were randomized to receive prophylactic administration of gabexate and 100 patients were randomized to the placebo group. Duodenal intubation was impossible in 7 patients, who were excluded from the study, leaving 98 patients in the gabexate group and 95 patients in the placebo group. The two groups were similar with regard to sex, mean age, indications for ERCP, occurrence of risk factors, and difficulty of ERCP (Table 1).

Incidence of post-ERCP pancreatitis

Acute pancreatitis developed in 13 patients after ERCP, with an overall incidence of 6.7% (Table 2). Patients treated with gabexate had a lower incidence of pancreatitis than those treated with placebo (3.1 *vs* 10.5%, respectively), with a significant difference between groups ($P = 0.040$; Table 2). Acute pancreatitis was clinically mild and edematous.

Incidence of hyperamylasemia

Patients treated with gabexate had a lower incidence of hyperamylasemia than those treated with placebo (33.7 *vs* 43.7%, respectively), but the difference was not significant ($P = 0.133$; Table 2).

Incidence of pancreatic pain

Patients treated with gabexate had a lower incidence of pancreatic pain than those treated with placebo (15.3 *vs* 29.5%, respectively), with the difference being significant ($P = 0.018$; Table 2).

Table 1. Characteristics of the patients studied.

	Placebo	Gabexate
Demographic characteristics		
Patient number	95	98
Sex (male/female)	44/51	46/52
Age (years)	64 ± 16	60 ± 15
Main indications for ERCP		
Bile duct calculus	58	64
Cholestatic jaundice	14	22
Cholangitis	6	14
Biliary pain	17	24
Risk factors for post-ERCP pancreatitis		
Age <35 years	4	2
History of acute pancreatitis	6	12
Common bile duct diameter <8 mm	26	30
Suspected sphincter of Oddi dysfunction	6	10
Pre-cut	4	10
Difficulty of ERCP		
Persistence time (min)	40.5 ± 16.8	37.7 ± 15.3
Therapeutic ERCP	80	87

Data are reported as number of patients or mean ± SD. ERCP = endoscopic retrograde cholangiopancreatography. There were no statistical differences between groups ($P > 0.05$, chi-square test for enumeration data and Student *t*-test for measurement data).

Table 2. Incidence of post-ERCP pancreatitis, hyperamylasemia, and pancreatic pain in the patients studied.

	Placebo	Gabexate	P value
Pancreatitis	10 (10.5%)	3 (3.1%)	0.040
Hyperamylasemia	42 (43.7%)	33 (33.7%)	0.133
Pancreatic pain	28 (29.5%)	15 (15.3%)	0.018

Data are reported as number of patients and percent in parentheses. The chi-square test was used for statistical comparison. ERCP = endoscopic retrograde cholangiopancreatography.

Other complications and adverse events

Some other complications such as bloating, nausea, vomiting, or fever were observed in both groups, with no significant difference between them. There was no adverse event associated with the use of gabexate.

Discussion

ERCP is an endoscopic technique that has been applied for more than 30 years for imaging biliary and pancreatic ducts. ERCP is valuable for the management of pancreatic and biliary diseases because it allows the physician to perform therapeutic procedures (e.g., gallstone extraction, biliary drainage, stent placement) at the time of diagnosis (7). Pancreatitis is a complication that has plagued ERCP since its inception.

Reported rates of pancreatitis after ERCP and sphincterotomy range from less than 1 to 40%, but rates of 5% or more are typical (8). However, the incidence is a little higher in some areas such as China (about 10-15%) (9,10). The underlying reason is unclear. This fact also indicates the importance of finding a more cost-effective drug to prevent post-ERCP pancreatitis in such areas. Variations in the reported rates of pancreatitis are related to many factors including the definition used, the thoroughness of follow-up, and patient- and technique-related risk factors. In the consensus classification (5), pancreatitis is defined as a clinical syndrome consistent with pancreatitis (i.e., new or worsened abdominal pain) with amylase levels at least three times higher than normal at more than 24 h after the procedure, and requiring more than one night of hospitalization. Some events are difficult to classify in the consensus definition, such as patients with post-procedural abdominal pain and elevation of amylase to levels just under three times normal ones, or patients with dramatic amylase elevations but minimal symptoms that are not clearly suggestive of clinical pancreatitis.

A combination of several technical and patient factors may play a role in the onset of pancreatic injury after ERCP (11,12). Important technical factors include papillary trauma and edema caused by repeated probing with a cannula or guide wire (especially in patients where biliary or pancreatic cannulation is difficult), pancreatic sphincterotomy, precut sphincterotomy, and balloon dilation of the biliary sphincter. Patient characteristics that increase the risk of post-ERCP pancreatitis are female gender, age <35 years, suspected sphincter of Oddi dysfunction, non-dilated bile duct, and previous post-ERCP pancreatitis. The mechanism by which these variables predispose to pancreatitis after ERCP is unclear.

Several approaches have been taken toward avoiding this complication: pharmacological prevention, patient selection (avoiding high-risk patients) and the placement of transsphincteric pancreatic stents (13). The ideal prophylactic agent should have the following characteristics: i) be effective in the majority of patients; ii) be inexpensive; iii) be able to be administered on the day of the procedure, and preferably 30-60 min before the procedure; iv) not requiring prolonged administration after the procedure, and v) not increasing the pressure of the sphincter of Oddi (14).

Gabexate is a synthetic, nonantigenic, 417-kDa protease inhibitor. It has a half-life of 55 s, is widely distributed and is eliminated in the inactive form by the kidneys. Gabexate inhibits trypsin, kallikrein and plasmin, thrombin, phospholipase A2, and C1 esterase (14). Studies on experimental animals and humans have demonstrated that prophylactic administration of gabexate prevents acute pancreatitis (15-17). In addition, in both animals and humans, gabexate has an inhibitory action on the sphincter of Oddi (18-20). An early study by our group (20) showed that infusion of gabexate, 1 and 3

mg kg^{-1} h^{-1}, did not affect basal pressure ($P > 0.05$) or the amplitude of phasic contraction ($P > 0.05$); it significantly reduced the frequency of contraction ($P < 0.05$), although there was no difference between gabexate infusion of 1 and 3 mg kg^{-1} h^{-1} ($P > 0.05$); high dose gabexate markedly reduced the motility index ($P < 0.01$) and there was a significant difference between gabexate infusion of 1 and 3 mg kg^{-1} h^{-1} as well ($P < 0.05$). These results suggest that gabexate could prevent post-ERCP pancreatitis due to its inhibitory effect on the motility of the sphincter of Oddi.

In a meta-analysis of 6 studies with a significant variation in the duration of infusion, Andriulli et al. (3) examined the incidence of acute pancreatitis, hyperamylasemia and pancreatic pain in 311 patients who received gabexate and 369 controls. Acute pancreatitis developed in 1.6% of patients in the gabexate group and in 6.5% of the controls (OR = 0.27, P = 0.001). The incidence of hyperamylasemia and pancreatic pain was also significantly lower in the gabexate group. Thus, gabexate was associated with significant improvements in all three outcomes. However, like somatostatin, gabexate is very expensive as a prophylactic agent since it needs to be given as an infusion for 12 h after ERCP, requiring overnight hospitalization. Moreover, in the same report, these investigators performed another meta-analysis that indicated that short-term infusion (<4 h) of gabexate may not reduce the incidence of post-ERCP pancreatitis.

In another study, Masci et al. (4) tested whether infusion of gabexate, at the same concentration but for a shorter period of time (6.5 h), was as effective as a 13-h infusion in preventing post-ERCP pancreatitis and observed that the overall incidence of acute pancreatitis, serum amylase and lipase values over time, peak levels of the two enzymes, pancreatic pain, and need for analgesics did not differ significantly between the two groups.

The most important result of the present study is that a 4.5-h infusion containing 300 mg gabexate significantly reduced the incidence of pancreatitis after ERCP: gabexate group, 3 of 98 (3.1%) *vs* control group, 10 of 95 (10.5%; P = 0.040, chi-square test). Pancreatic pain was reduced in the gabexate group compared to the control group, but the frequency of hyperamylasemia was not affected by the drug. The efficacy of gabexate for reducing post-ERCP pancreatitis has been demonstrated by others (3,4), but the present study used less gabexate and reduced the duration of infusion, thereby reducing the cost/effect ratio of the use of the drug and increasing its potential use.

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