

GABEXATE FOR THE PREVENTION OF PANCREATIC DAMAGE RELATED TO ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

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ABSTRACT

Background Endoscopic retrograde cholangiopancreatography (ERCP) is associated with elevated levels of pancreatic enzymes and pancreatitis. Gabexate, a protease inhibitor, has been used to prevent pancreatic damage related to ERCP.

Methods We conducted a multicenter, double-blind comparison of gabexate (1 g given by intravenous infusion starting 30 to 90 minutes before endoscopy and continuing for 12 hours afterward) with placebo (mannitol and sodium chloride, administered in the same fashion). A total of 435 adults scheduled to undergo ERCP and, when indicated, endoscopic sphincterotomy underwent randomization; 17 were excluded from the final analysis for various reasons. The remaining 418 patients (mean age, 60.4 years) — 208 in the gabexate group and 210 in the placebo group — were analyzed. Acute pancreatitis was considered to be present if serum amylase or lipase levels (or both) were five times greater than the upper limits of normal in association with the onset of pancreatic pain.

Results After the procedures, 276 patients (66 percent) had elevated pancreatic-enzyme levels; the frequency was similar in the two groups. Mean serum amylase values were higher in the placebo group than in the gabexate group through 24 hours of observation ($P=0.03$). Twelve patients in the gabexate group and 29 in the placebo group had abdominal pain (6 percent vs. 14 percent, $P=0.009$). Sixteen patients in the placebo group and five in the gabexate group had acute pancreatitis (8 percent vs. 2 percent, $P=0.03$). Two patients treated with gabexate and six given placebo had adverse events, all of which resolved. Two patients given placebo died of acute pancreatitis; one was excluded from the evaluation because pancreatitis was present before endoscopy. One patient in the gabexate group died, from a myocardial infarction.

Conclusions Prophylactic treatment with gabexate reduced pancreatic damage related to ERCP, as reflected by reductions in the extent but not the frequency of elevated enzyme levels and in the frequency of pancreatic pain and acute pancreatitis. (*N Engl J Med* 1996;335:919-23.)

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ENDOSCOPIC retrograde cholangiopancreatography (ERCP) is used to diagnose and treat diseases affecting the biliary and pancreatic tracts. Manipulation of the papilla of Vater, however, is associated with serum pancreatic-enzyme elevations in up to 70 percent of patients and with acute pancreatitis, which may be fatal in some instances.¹⁻⁶ Attempts to prevent these complications with aprotinin,⁷ glucagon,^{7,8} calcitonin,⁹ nifedipine,¹⁰ naturally occurring somatostatin,¹¹⁻¹⁴ and more recently, octreotide¹⁵⁻¹⁷ have been disappointing.

Gabexate (ethyl-guanidine-hexanoil-oxy-dibenzoate-methyl-sodium-sulfonate) is a synthetic compound of 417 daltons that is not antigenic¹⁸ and diffuses easily. When administered by continuous intravenous infusion, gabexate reaches a steady state within 15 minutes, with a half-life of 55 seconds,¹⁹ and is eliminated in inactive form by the kidney. Gabexate is a protease inhibitor, with effects on trypsin, kallikrein, and plasmin, even when bound to alpha₂-macroglobulin; on thrombin, even in the absence of antithrombin III; and on phospholipase A₂ and C1 esterase.¹⁸ In animals it prevents acute pancreatitis induced by various means.²⁰⁻²³ In Japan, gabexate has been used as prophylaxis against serum pancreatic-enzyme elevations^{20,24,25} and acute pancreatitis^{26,27} after endoscopic procedures. In these and other studies of the treatment of hyperenzymemia^{28,29} and acute pancreatitis,^{30,31} there were no serious side effects, even when the medication was given at high doses. We conducted a multicenter placebo-controlled trial to assess the ability of gabexate to prevent pancreatic damage due to endoscopic and therapeutic maneuvers involving the papilla of Vater.

METHODS**Patients**

This study was conducted in 17 digestive-endoscopy centers in Italy from July 1993 to October 1994. The study group consisted of patients over 18 years of age who were scheduled to undergo ERCP and, when indicated, endoscopic sphincterotomy (Table

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1). Exclusion criteria included active acute pancreatitis, chronic pancreatitis, pancreatic cancer, or cancer of the papilla of Vater. Patients with severe systemic diseases with possible secondary involvement of the pancreas or bile ducts were excluded, as were those being treated with drugs potentially capable of damaging the pancreas. Women of childbearing age, breast-feeding mothers, and women who were not using adequate contraception were also excluded. A total of 435 consecutive patients (236 women and 199 men; mean [\pm SD] age, 60 ± 23 years) scheduled to undergo ERCP, endoscopic sphincterotomy of Oddi's sphincter, or both were recruited. All patients gave written informed consent before study entry. The study was approved by the ethics committee at each center. Data are not available on screened patients who did not meet the entry criteria.

Study Design

A thorough clinical history was elicited from all patients enrolled in the study, and the reasons for the endoscopic examination were emphasized. For each patient, 10 identical-appearing vials that contained 100 mg of gabexate (Foy, Lepetit, Lainate, Italy) or placebo (mannitol and sodium chloride) were packaged according to a centralized randomization schedule. The contents of all 10 vials (total dose, 1 g) were dissolved in 500 ml of a 0.9 percent saline solution or a 5 percent glucose solution and administered by continuous intravenous infusion beginning 30 to 90 minutes before the endoscopy session and continuing for 12 hours afterward. Patients and physicians were unaware of the treatment assignments. Therapy with antibiotics, analgesics, and sedatives was allowed, whereas concomitant therapy with aprotinin, somatostatin, or octreotide or major morphine or morphine-like analgesics was a reason for exclusion. Benzodiazepines, spasmolytic agents, and atropine, alone or in combination, were allowed for premedication. All patients began fasting at midnight on the day before the examination. The contrast medium used during the endoscopic maneuvers was iopamidol (Iopamir, Bracco, Milan, Italy), a low-osmolality, non-ionic substance. At the end of the session, the endoscopist recorded the details of the endoscopic maneuver performed (including procedures such as endoscopic sphincterotomy), the ease or difficulty of cannulating the papilla of Vater, the appearance of the pancreatic duct (i.e., whether it was

opacified), and the results of parenchymographic radiologic imaging, if performed. After endoscopy, patients fasted for at least eight hours. Serum amylase and lipase were measured before endoscopy and 4, 8, 12, and 24 hours afterward. The presence of abdominal pain attributable to the pancreas and the use and type of analgesic therapy were also recorded at these times. Ultrasonography was performed when pain occurred or when serum enzyme levels were five times higher than normal. If ultrasonography failed to detect abnormalities or foci of necrosis or peripancreatic collections were present, abdominal computed tomography was performed.

Definitions

Hyperenzymemia was defined as an elevation of serum amylase or lipase levels (or both) above the upper limits of normal if basal enzyme levels were normal or as any further elevation in these enzymes if basal enzyme levels exceeded the upper limits of normal. The peak value was the highest level of amylase or lipase recorded at any time. Pancreatic pain was defined as persistent pain in the epigastrium and periumbilical region and often radiating to the back. Acute pancreatitis was considered to be present if serum amylase or lipase levels (or both) were five times greater than the upper limits of normal in association with the onset of pancreatic pain. The study end points were reductions in the incidence or extent of hyperenzymemia, pancreatic pain, and acute pancreatitis after ERCP.

Statistical Analysis

When appropriate we used the chi-square test (with Yates' correction) and Fisher's exact test for categorical comparisons of data. Serum amylase and lipase data were subjected to analysis of variance for split-plot design with repeated measures (SAS version 6.04, GLM program).

RESULTS

Of the 435 patients enrolled, 215 were treated with gabexate and 220 with placebo. Seventeen patients (7 in the gabexate group and 10 in the placebo group) were subsequently excluded from the final evaluation for the following reasons: the examination was not performed (2 patients in the gabexate group and 3 in the placebo group), acute pancreatitis was present at the time of the examination (3 patients in the placebo group), concomitant treatment with octreotide was being administered (3 patients in the placebo group), and data were not complete (5 patients in the gabexate group and 1 in the placebo group). This left 418 patients, 208 in the gabexate group and 210 in the placebo group. The groups were similar with regard to sex, age, body-mass index (the weight in kilograms divided by the square of the height in meters), and indication for endoscopy (Table 1).

Frequency of Hyperenzymemia

Before ERCP, 328 patients (78 percent) had serum amylase or lipase concentrations (or both) within the upper limits of normal (163 in the gabexate group and 165 in the placebo group, $P=0.95$) and 90 patients (22 percent) had elevated basal serum enzyme levels (45 in each group). After ERCP, 276 patients (66 percent) had hyperenzymemia. The frequency of hyperenzymemia was lower among patients with normal basal enzyme levels than among those with ele-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 418 PATIENTS.*

CHARACTERISTIC	GABEXATE GROUP (N=208)	PLACEBO GROUP (N=210)
Sex (M/F)	88/120	98/112
Age (yr)	60.1 \pm 15.0	60.6 \pm 16.9
Body-mass index†	24.8 \pm 3.6	24.8 \pm 3.6
Indications for ERCP (no. of patients)		
Choledocholithiasis	67	86
Intrahepatic lithiasis	6	5
Stenosis of the papilla	11	15
Biliary stenosis	38	25
Cholangitis	40	49
Biliary pain	111	111
Dyskinesia of Oddi's sphincter	5	4
Previous acute pancreatitis	28	22
Recurrent pancreatitis	3	3

*Plus-minus values are means \pm SD. ERCP denotes endoscopic retrograde cholangiopancreatography.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

vated levels (188 of 328 vs. 88 of 90 patients, or 57 percent vs. 98 percent; $P < 0.001$). Hyperenzymemia was more common after imaging of the pancreatic ducts than after bile-duct imaging (162 of 234 vs. 101 of 167 patients, or 69 percent vs. 60 percent; $P = 0.08$). Hyperenzymemia followed 13 of the 17 unsuccessful procedures (76 percent). The frequency of hyperenzymemia was similar whether endoscopic sphincterotomy or only diagnostic procedures were performed (156 of 232 vs. 120 of 186 patients, or 67 percent vs. 65 percent; $P = 0.63$). The frequency of hyperenzymemia did not vary between the groups for any of the endoscopic maneuvers.

Degree of Hyperenzymemia

After ERCP, the mean (\pm SE) peak levels of amylase and lipase were similar in patients with normal basal enzyme levels and those with elevated basal levels (amylase, 650.2 ± 69.9 and 777 ± 140.5 U per liter, respectively; $P = 0.43$; lipase, 1190 ± 196.2 and 1060 ± 290.9 U per liter; $P = 0.75$). The addition of endoscopic sphincterotomy was not associated with a marked increase in enzyme levels above that associated with diagnostic maneuvers (amylase, 767 ± 111 and 602 ± 68.7 U per liter, respectively; $P = 0.20$; lipase, 1340 ± 265 and 1013 ± 209 U per liter; $P = 0.34$). After the procedures, serum amylase values were significantly higher in the placebo group than in the gabexate group through 24 hours of observation ($P = 0.03$) (Fig. 1). A similar pattern was observed for lipase (data not shown), but the differences were not significant ($P = 0.09$).

Pain and Hyperenzymemia

Forty-one patients (10 percent) had abdominal pain after the procedure. The frequency was significantly higher in the placebo group than in the gabexate group (14 percent vs. 6 percent, $P = 0.009$) (Table 2). Ninety percent of the patients with pain had hyperenzymemia (37 of 41), as compared with 63 percent of asymptomatic patients (239 of 377, $P = 0.001$). The mean peak amylase and lipase values were higher in the symptomatic patients than in the asymptomatic patients (amylase, 1861 ± 340 vs. 546 ± 56 U per liter; $P < 0.001$). All 29 symptomatic patients in the placebo group had hyperenzymemia, as compared with 8 of the 12 in the gabexate group (67 percent, $P = 0.004$). Gabexate was not associated with any difference in the frequency of hyperenzymemia in asymptomatic patients (126 of 196 patients in the gabexate group vs. 113 of 181 patients in the placebo group, or 64 percent vs. 62 percent; $P = 0.79$). Pain was more frequent after pancreatic-duct imaging than after bile-duct imaging (33 of 234 vs. 7 of 167 patients, or 14 percent vs. 4 percent; $P = 0.001$). Pain was also more frequent after operative procedures than after diagnostic examination (24 of 186 vs. 17 of 232 patients, or 13 percent vs. 7 percent; $P = 0.08$).

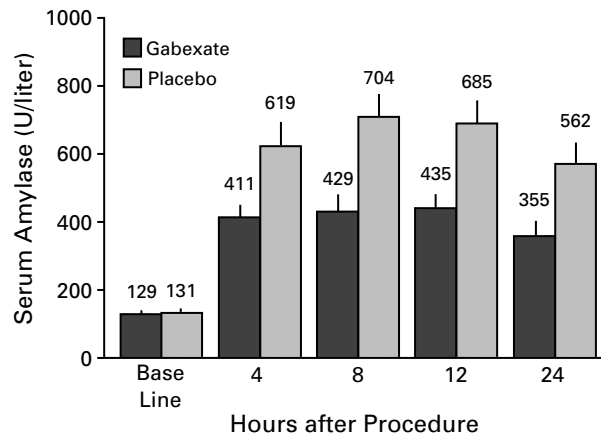


Figure 1. Mean (\pm SE) Serum Amylase Levels before and after Endoscopic Procedures in Patients Treated with Gabexate (N=207) or Placebo (N=208).

The mean level is shown above each bar. Data were missing for three patients.

Acute Pancreatitis

The overall incidence of acute pancreatitis was 5 percent. Patients treated with gabexate had a lower incidence of acute pancreatitis than those given placebo (2 percent vs. 8 percent, $P = 0.03$) (Table 2). Endoscopies that included pancreatic-duct imaging were associated with acute pancreatitis in 6 percent of patients (15 of 234); in contrast, in endoscopies involving bile-duct imaging alone, only 3 percent of patients had pancreatitis (5 of 167, $P = 0.18$) (Table 3). The incidence of acute pancreatitis was similar after diagnostic procedures and procedures including sphincterotomy (5 percent vs. 5 percent, $P = 0.94$) (Table 3). The incidence of acute pancreatitis was similar among patients with normal basal enzyme levels and those with elevated levels (17 of 328 and 4 of 90 patients, respectively; 5 percent and 4 percent; $P = 0.99$).

Acute pancreatitis was clinically mild and of the edematous type, as assessed by ultrasonography or computed tomography, in 16 of the 21 patients (76 percent) and of the necrotizing type in the remaining 5 patients (24 percent). All five patients with pancreatitis in the gabexate group had mild disease that resolved with only medical measures. By contrast, 5 of the 16 patients with acute pancreatitis in the placebo group had necrotizing pancreatitis. Three of these five patients had peripancreatic fluid collections, for which one required surgery and subsequently died of multiorgan failure on day 19.

Need for Analgesics, Ultrasonography, and Computed Tomography

More patients required analgesics in the placebo group than in the gabexate group (24 of 199 vs. 12

TABLE 2. INCIDENCE OF HYPERENZYMEMIA, PAIN, AND ACUTE PANCREATITIS IN THE TREATMENT GROUPS.

VARIABLE	GABEXATE GROUP (N=208)	PLACEBO GROUP (N=210)	TOTAL (N=418)
Hyperenzymemia	134 (64)	142 (68)	276 (66)
Pain	12 (6)*	29 (14)	41 (10)
Acute pancreatitis	5 (2)†	16 (8)	21 (5)

*P=0.009 for the comparison with the placebo group.

†P=0.03 for the comparison with the placebo group.

TABLE 3. PERCENTAGE OF PATIENTS WITH ACUTE PANCREATITIS AFTER VARIOUS ENDOSCOPIC PROCEDURES.

TREATMENT	GABEXATE GROUP	PLACEBO GROUP	TOTAL
Pancreatic-duct imaging	4/115 (3)	11/119 (9)	15/234 (6)
Bile-duct imaging	1/83 (1)	4/84 (5)	5/167 (3)
Unsuccessful imaging	0/10	1/7 (14)	1/17 (6)
Diagnostic procedure	3/113 (3)	8/119 (7)	11/232 (5)
Operative procedure	2/95 (2)	8/91 (9)	10/186 (5)

of 199 patients for whom information was available, or 12 percent vs. 6 percent; $P=0.05$). Ultrasonography was performed in 54 patients in the placebo group as compared with 29 in the gabexate group (26 percent vs. 14 percent, $P=0.003$). Seven patients in the placebo group and three in the gabexate group underwent computed tomography.

Adverse Events and Mortality

Eight patients — two in the gabexate group and six in the placebo group — had adverse events during the treatment. One of the patients in the gabexate group had mild nausea and vomiting, and the other had self-limiting dyspnea and a hypertensive crisis; all these effects resolved with no interruption of treatment. The six patients in the placebo group had eight adverse events: flushing in two, vomiting in three, hypotension in one, sweating in one, and malaise in one. Three patients died, two in the placebo group and one in the gabexate group. One patient in the placebo group died of acute pancreatitis, which was present before endoscopy, and was excluded from the final evaluation. Another patient in the placebo group, as discussed above, died 19 days after endoscopy of multiorgan failure due to acute pancreatitis. The patient in the gabexate group died of a myocardial infarction 14 days after endoscopy.

DISCUSSION

Prophylactic treatment with gabexate reduced pancreatic damage related to endoscopic maneuvers involving the papilla of Vater, as reflected by reductions in the extent but not the frequency of hyperenzymemia and in the frequency of pain and acute pancreatitis. The incidences of hyperenzymemia, pain, and acute pancreatitis in particular in the placebo group — 68 percent, 14 percent, and 8 percent, respectively — are similar to those in other prospective studies.^{4,32} The incidence of adverse effects associated with endoscopic retrograde cholangiopancreatography was higher than that reported in a number of retrospective studies⁴; this difference may be attributable to a greater awareness of the problem and to better recording of data in prospective studies.^{2,4} Almost all the patients with elevated serum enzyme levels at base line had further increases in amylase, lipase, or both, but as reported previously,¹ the extent of the increase and the frequency of acute pancreatitis were similar to those in patients with normal enzyme levels at base line. These data confirm the hypothesis^{1,33} that high initial pancreatic-enzyme levels are not necessarily a contraindication to endoscopy.

Treatment with gabexate did not lower the frequency of hyperenzymemia but did reduce the extent of the increase in enzyme levels. The pancreatic damage that ensues after manipulation of the papilla of Vater may be due to extraductal leakage of the pancreatic juice present in the ducts, traumatic rupture of a number of acinar units,^{1,2,4} or alterations of the acinar cells. Such functional alterations, caused by the temporary obstruction of the ducts, consist of a block in the normal cellular exocytosis of enzymes, which instead leak into the interstitium and then into the blood.^{34,35} As a protease inhibitor and a diffusible molecule, gabexate may help contain the increase in enzymes due to functional alterations of the acinar cell. Studies in rats²⁰ have demonstrated that prophylactic administration of gabexate prevents alterations in intracellular transport and the elevation in serum amylase levels, probably by blocking an esterase involved in these changes. In our study, treatment with gabexate appeared to reduce not only the frequency and severity of the pain (as shown by the less frequent use of analgesics), but also the frequency of hyperenzymemia in symptomatic patients. It did not, however, affect the frequency of hyperenzymemia in people without pain. In conclusion, our results demonstrate that prophylactic administration of gabexate reduces the frequency of acute pancreatitis after operative and diagnostic endoscopic maneuvers on the papilla of Vater. Further studies are necessary to identify the patients at greatest risk for acute pancreatitis and to evaluate the cost effectiveness of this therapy.

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APPENDIX

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