Nafamostat for Prophylaxis against Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis Compared with Gabexate

Jae Hyuck Chang, In Seok Lee, Hyung Keun Kim, Yu Kyung Cho, Jae Myung Park, Sang Woo Kim, Myung-Gyu Choi, and In-Sik Chung

Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background/Aims: The protease inhibitors, nafamostat and gabexate, have been used to prevent pancreatitis related to endoscopic retrograde cholangiopancreatography (ERCP). In vitro, nafamostat inhibits the pancreatic protease activities 10-100 times more potently than gabexate. We evaluated the efficacy of nafamostat for prophylaxis against post-ERCP pancreatitis in comparison with gabexate.

Methods: Five hundred patients (208 patients in the nafamostat-treated group and 292 in the gabexate-treated group) were analyzed retrospectively after selective exclusion. The incidences of pancreatitis and hyperamylasemia after the ERCP were compared between the nafamostat and gabexate groups.

Results: The incidences of acute pancreatitis and hyperamylasemia were 9.1% and 40.9%, respectively, in the nafamostat-treated group, and 8.6% and 39.4% in the gabexate-treated group. The frequencies of post-ERCP pancreatitis and hyperamylasemia did not differ significantly between the two groups. Post-ERCP pancreatitis in two group did not vary according to the different ERCP procedures. The mean serum amylase level at 6 h after ERCP was significantly lower in the nafamostat-treated group than in the gabexate-treated group (p=0.020). However, the difference in serum amylase level did not persist at 18 h and 36 h post-ERCP.

Conclusions: Administration of nafamostat before ERCP was not inferior to gabexate in protecting against the development of pancreatitis. (Gut and Liver 2009;3:205-210)

Key Words: Gabexate; Nafamostat; Endoscopic retrograde cholangiopancreatography; Pancreatitis; Hyperamylasemia

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an important procedure for the diagnosis and treatment of biliary and pancreatic conditions. Prospective studies show that acute pancreatitis occurs in 3-17% of cases following the ERCP and that the post-ERCP pancreatitis (PEP) is associated with substantial morbidity, and even with mortality.1-3 Although PEP in most cases are mild, 10% of cases progress to severe pancreatitis, resulting in prolonged hospital stays and life-threatening consequences.3

Several attempts have been made to minimize the occurrence and severity of PEP; identifying high-risk patients, developing less traumatic endoscopic interventions to limit pancreatic injury, and finding effective pharmacologic agents to administer prophylactically before ERCP. The efficacy of such agents (somatostatin, octreotide, diclofenac, indomethacin, and gabexate mesylate) to reduce the risk of PEP had been studied extensively.4-7

Although the pathophysiologic precipitant of acute pancreatitis remains unclear, it has been demonstrated in an animal model which stimulation of exocrine pancreatic secretion leads to further deterioration of acute pancreatitis.8 Premature intracellular activation of proteolytic enzymes results in autodigestion, impaired acinar secretion, and local inflammatory responses.9

Nafamostat (FUT-175; 6-amidino-2-naphthyl p-guanidino-benzoate dimethane-sulfonate) is a low molecular weight protease inhibitor that inhibits serine proteases (such as trypsin), kallikrein, C1r and C1s, complement activation, thrombin, and plasmin.10 Nafamostat had been
shown to be 10-100 times more potent than gabexate in in vitro experiments, and it was more effective than gabexate in the treatment of necrotizing pancreatitis in a rat model. Nafamostat has been used for the treatment of severe pancreatitis or prophylaxis against pancreatitis after endoscopic procedures, and no serious side effects were reported. However, nafamostat has scarcely been studied for the prophylaxis against post-ERCP pancreatitis.

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

MATERIALS AND METHODS

1. Patients

Between 2005 and 2007, 1,074 patients undergoing ERCP in the gastrointestinal endoscopy unit of Kangnam St. Mary’s Hospital (a tertiary referral center) were consecutively enrolled and analyzed retrospectively. Nafamostat or gabexate was administered intravenously to 500 patients to prevent post-ERCP pancreatitis. Patients with naïve ampulla of Vater were included. Exclusion criteria were as follows: age <18 years, previous surgery (Billroth II gastrectomy, Roux-en-Y anastomosis, and choledocho-jejunostomy), previous sphincterotomy or biliary stenting, stenting into pancreatic duct, acute pancreatitis before ERCP, and combined use of octreotide or somatostatin.

This study was approved by the Institutional Review Board of our hospital. Patient’s anonymity was preserved and the study protocol confirmed to the Declaration of Helsinki as revised in Edinburg in 2000.

2. Administration of nafamostat or gabexate and follow-up

Six hundred mg of gabexate (Foy®, Dong-A Pharm, Seoul, Korea) or 50 mg of nafamostat (Futhan®, SK Chemical Life Science, Seoul, Korea) was dissolved in 5% glucose solution and administered by continuous intravenous infusion beginning 30 minutes before the endoscopy session and continuing for 12 hours afterwards. Therapy with antibiotics, analgesics, and sedatives was permitted, whereas concomitant therapy with somatostatin or octreotide was a basis for exclusion. Benzodiazepines, anti-spasmodic agents, and non-narcotic analgesics, alone or in combination, were also allowed. Ioxitalamic acid (Telebrix®, Guerbet, Roissy CdG Cedex, France), a water-soluble, monomeric, ionic contrast medium was used during the endoscopic maneuvers. One experienced senior endoscopist, with a career experience of over 1,000 ERCPs and an annual ERCP caseload of over 300, directly performed or supervised all the procedures. If the cannulation or a therapeutic procedure by a fellow-in-training was unsuccessful, the supervisor assumed the procedure. After endoscopy, patients were to in fasting state for at least 18 hours. Serum amylase was measured before endoscopy and 6, 18, and 36 hours afterward. The presence of abdominal pain attributable to the pancreas and the use and type of analgesic therapy at those times were evaluated.

3. Definition

The definition of pancreatitis was based on the consensus criteria. Post-ERCP pancreatitis was defined as the followings: a newly developed or increased abdominal pain within 24 hours after ERCP requiring analgesic agents, and the elevation of serum amylase level at least three times of normal upper limit around 18 hours after the procedure (the next morning). The severity was graded mild when hospitalization lasted 2 to 3 days, moderate when 4 to 10 days, and severe when hospitalization was prolonged for more than 10 days or any of the following occurred: hemorrhagic pancreatitis, pancreatic necrosis, pancreatic pseudocyst, or a need for percutaneous drainage or surgery. Hyperamylasemia was defined as an elevation of serum amylase level in the morning after ERCP above the upper limit of normal if basal enzyme level was normal or as any further elevation in the enzyme if basal enzyme level exceeded the upper limit of normal. Visualization of the entire pancreatic duct by contrast injection was regarded as pancreatic duct injection. Precut was performed at periampullary area and infundibulotomy was not performed.

4. Statistical analysis

The chi-square test was used for comparisons of categorical data and student t-test was used for comparisons of continuous data. Serum amylase data after ERCP were subjected to student t-test at each time after ERCP and to analysis of variance with repeated measures (repeated measures ANOVA) through the follow-up duration. The statistical analyses were performed using SPSS, version 14.0 (SPSS Inc., Chicago, IL, USA). p-values <0.05 were considered significant.

RESULTS

Five hundred patients were enrolled in the study after exclusion criteria were applied; 208 patients were in the nafamostat group and 292 patients in the gabexate group. The mean age was 61.1±15.0 years and 220 (44%) pa-