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RAPID COMMUNICATION

N-acetylcysteine does not prevent post-endoscopic retrograde cholangiopancreatography hyperamylasemia and acute pancreatitis

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Abstract

AIM: Acute pancreatitis (AP) is the most common and often severe complication of endoscopic retrograde cholangiopancreatography (ERCP). The early step in the pathogenesis of acute pancreatitis is probably the capillary endothelial injury mediated by oxygen-derived free radicals. N-acetylcysteine - a free radical scavenger may be potentially effective in preventing post-ERCP acute pancreatitis and it is also known that N-acetylcysteine (ACC) can reduce the severity of disease in experimental model of AP.

METHODS: One hundred and six patients were randomly allocated to two groups. Fifty-five patients were given N-acetylcysteine (two 600 mg doses orally 24 and 12 h before ERCP and 600 mg was given iv, twice a day for two days after the ERCP). The control group consisted of 51 patients who were given iv. isotonic saline twice a day for two days after the ERCP. Serum and urine amylase activities were measured before ERCP and 8 and 24 h after the procedure. The primary outcome parameter was post-ERCP acute pancreatitis and the secondary outcome parameters were differences between groups in serum and urine amylase activity.

RESULTS: There were no significant differences in the rate of post-ERCP pancreatitis between two groups (10 patients overall, 4 in the ACC group and 6 in the control group). There were also no significant differences in baseline and post-ERCP serum and urine amylase activity between ACC group and control group.

CONCLUSION: N-acetylcysteine fails to demonstrate any significant preventive effect on post-ERCP pancreatitis, as well as on serum and urine amylase activity.

Key words: N-acetylcysteine; ERCP; Acute pancreatitis; Hyperamylasemia

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INTRODUCTION

Since their introduction, endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) have played a very important role in the diagnosis and treatment of biliary and pancreatic diseases. Magnetic resonance cholangiopancreatography (MRCP) is a very safe procedure and capable of providing diagnostic information similar to ERCP, but ERCP and EST still hold a key therapeutic role[1-3]. Although these procedures are generally considered being safe, they are associated with some complications, like cholangitis, haemorrhage, perforation and acute pancreatitis (AP). Acute pancreatitis is the most frequent major complication of ERCP. It is estimated that it occurs in 1%-15% of patients overall[4,5], with a higher incidence in subjects who have had therapeutic ERCP[6].

Post-ERCP pancreatitis usually is defined as new onset of abdominal pain persisting for more than 24 h after the procedure, and elevation of serum pancreatic enzymes 5 times above the normal limit. Asymptomatic increase in pancreatic enzyme activities may occur in up to 70% of all cases. Although the pathogenesis of post-ERCP pancreatitis is not clearly understood, it seems that the patient's inflammatory response to pancreatic

duct imaging and instrumentation plays a critical role[5]. An early step in the pathogenesis of acute pancreatitis is capillary endothelial injury manifested as increased capillary permeability[7]. An experimental study suggested that capillary injury might be mediated by oxygen-derived free radicals[8]. The manifestations of pancreatitis in experimental animal model can be ameliorated by blocking the action of oxygen-derived free radical scavengers[9-11]. Acetylcysteine is an excellent source of sulfhydryl groups, and is converted in the body into metabolites capable of stimulating glutathione synthesis and acting directly as free radical scavenger[12]. It has been shown that acetylcysteine can reduce severity of experimental acute pancreatitis[9,13,14]. Anecdotal reports suggest also that NAC could be effective in reducing complication of AP in humans[15]. N-acetylcysteine thus may be potentially effective in the prevention of post-ERCP acute pancreatitis.

Recently Katsinelos *et al*[16] have found that intravenous N-acetylcysteine does not prevent post-ERCP pancreatitis. The authors have pointed out that their findings cannot be generalized because larger cohorts may be needed to definitevly elucidate this problem. As combination of data from multiple, small (even underpowered) trials should enhance the precision and accuracy of any meta-analysis[17], we describe here the results of a prospective, randomized open-label study to determine the effect of N-acetylcysteine on the incidence of hyperamylasemia and pancreatitis after ERCP, which was previously reported only in the abstract form[18].

MATERIALS AND METHODS

Patients

Between January and December 2002, 345 consecutive patients undergoing ERCP in our institution were assessed for eligibility to enter the study. A total of 106 patients who fulfilled the entry criteria and gave their consent, were enrolled into the study. Exclusion criteria were as follows: presence of acute pancreatitis and/or severe chronic pancreatitis and/or hyperamylasemia, pregnancy and breast feeding, age under 18.

Patients were randomized to one of the two groups. In the treated group, 55 subjects received N-acetylcysteine (*ACC 600*, Hexal-Polska). Two 600 mg doses were given orally 24 h and 12 h before ERCP and 600 mg was given intravenously, twice a day for two days after the ERCP. The control group consisted of 51 patients who were given iv isotonic saline twice a day for two days after the ERCP. The present study was approved by the local ethics committee.

Endoscopic procedure

All endoscopic procedures were performed by the same experienced endoscopist. As a contrast medium 60% dilution of diatrizoate meglumine was used. All patients were fasted overnight and remained fasting for a minimum of 12 h after the ERCP. Patients stayed in the hospital for at least 48 h after the procedure. Biochemical parameters and clinical status were examined. Premedication consisted of pharyngeal anesthesia with xylocaine spray and intravenous administration of midazolam and hyoscine-N-butyl bromide titrated according to age and tolerance. ERCP was performed with the patient under general anesthesia with propofol and fentanyl, without airway intubation. At the end of each procedure, the endoscopist recorded also the details of the maneuvers performed, especially the ease or difficulty of cannulation, number of cannulations, number of pancreatic duct injections, presence of parenchymogram on radiography, or whether a needle-knife sphincterotomy was performed. Biochemical and clinical evaluation, serum and urine amylase activity were measured before ERCP and after 8 and 24 h of the procedure. Before the endoscopic procedure and 24 h after, blood samples were analysed for alanine and asparagine transaminases, bilirubin and white blood cells (leukocytosis was defined as a white cell count greater than 10000/ mm^3). The primary outcome parameter was frequency of AP post-ERCP, defined by clinical features consistent with acute pancreatitis beginning after ERCP and lasting for at least 24 h, associated with increase in serum amylase levels greater than five times above normal.

Secondary outcome parameters were differences between groups in serum and urine amylase activities measured at 8 and 24 h after the ERCP.

Table 1 Indications for ERCP in N-acetylcysteine treated group (ACC-group) and control group

ERCP indications	ACC group	Control group	*P*
Bile duct stones	35	32	NS
Recurrent pancreatitis	2	4	NS
Biliary pain, cholestasis	3	5	NS
Chronic pancreatitis	8	3	NS
Pancreatic cancer	3	1	NS
Other	4	6	NS

Statistical analysis

Univariate statistical analysis was performed using chi-square test, Fisher's exact test for count data or Student's *t*-test for comparison of means. Multivariate analysis was performed using forward logistic regression procedure and 0.05 and 0.1 as values to enter or remove the variables. Serum and urine amylase data were subjected to repeated measure analysis of variance with N-acetylcysteine treatment as between subject factor. $P < 0.05$ was considered statistically significant. The STATA software, version 8.2 for Macintosh (Stata Corporation, College Station, TX, USA) was used for statistical computations.

RESULTS

Of the 106 patients included, 55 were randomized to the ACC group and 51 to the control group. The groups were similar with respect to the main indications for ERCP (Table 1) and endoscopic procedures performed (Table 2). There were no significant differences in acute pancreatitis risk factors (female gender, multiple cannulations, pancreatic duct injections, precut papillotomy, common biliary duct diameter; diagnostic ERCP and failed procedure) between the groups (Table 3). Post-ERCP pancreatitis graded as mild or moderate was observed in 10 (9.4%) patients, 4

Table 2 ERCP procedure performed

ERCP procedure (patients)	ACC group	Control group
Diagnostic	4	2
Therapeutic	51	49
Endoscopic sphincterotomy	44	47

Table 3 Risk factors for acute pancreatitis

Risk factors (patients)	ACC group	Control group	Total	*P*
Gender (F/M)	33/22	33/18	66/40	NS
Multiple cannulations	9	7	16	NS
Pancreatic duct injections	13	12	25	NS
Diagnostic ERCP	5	1	6	NS
Failed procedure	2	3	5	NS
Precut papillotomy	12	9	21	NS
Small bile duct diameter	2	5	7	NS

Table 4 Unvariate analysis of group differences according to the presence of acute pancreatitis

Variables	Acute pancreatitis (*n* = 10)	No acute pancreatitis (*n* = 96)	*P*
N-acetylcysteine / Control	4/6	51/54	NS
Sex (F/M)	9/1	57/39	NS
Precut (Y/N)	6/4	15/81	0.004
Small bile duct diameter (Y/N)	1/9	6/90	NS
Multiple cannulations (Y/N)	5/5	11/85	0.006
Pancreatic duct injections (Y/N)	4/6	21/75	NS
Diagnostic ERCP (Y/N)	1/9	5/91	NS

(7.3%) patients in the ACC group and 6 (11.8%) in the control group (NS). In univariate analysis of differences between two groups according to the presence of acute pancreatitis, only two factors were significantly associated with an increased risk of pancreatitis: precut papillotomy and multiple cannulations. Female sex was on the verge of statistical significance (Table 4).

There were no significant differences in baseline and post-ERCP serum and urine amylase activity between ACC group and control group (Table 5). There were also no differences in total bilirubin, alanine and aspartate aminotransferases and WBC between the two groups (data not shown).

Initially the following variables including N-acetylcysteine treatment, precut papillotomy, multiple cannulations, common biliary duct diameter, injection of the contrast into pancreatic duct, failed procedure, sex and age, were entered into a logistic regression model.

On multiple logistic regression analysis, only precut papillotomy remained as a predictor of acute pancreatitis (Table 6).

DISCUSSION

Although certain risk factors have been identified, the development of post-ERCP pancreatitis remains unpredictable. The knowledge of risk factors for post-ERCP pancreatitis is often not helpful in avoiding pancreatitis in individual patients. For these reasons it would be beneficial to find prophylactic treatment capable of preventing post-ERCP pancreatitis. The present study was conducted to test the hypothesis that N-acetylcysteine might reduce the frequency and intensity of post- ERCP pancreatitis. Our results did not support this hypothesis. Similarly many other therapeutic agents including octreotide, low-molecular weight heparin, nifedipine, have no beneficial effect on the frequency of post-ERCP pancreatitis[19-26]. On the other hand, there are data suggesting that gabexate mesylate, diclofenac and heparin may reduce the frequency of post-ERCP pancreatitis[5,27-30]. Data concerning corticosteroids, IL-10 and somatostatin are contradictory[19, 31-33].

Oxygen reactive species (ROS) have been implicated in the initiation of acute pancreatitis[34]. Animal models of acute pancreatitis point out to the occurence of early and profound oxidative stress[35,36]. In human studies of acute pancreatitis, increased blood concentrations of the superoxide radical and lipid peroxides, as well as depletion of ascorbic acid and an increased fraction of dehydroascorbic acid have been found[37].

In experimental pancreatitis various forms of scavenger therapy for ROS, have been shown to mitigate the pancreatic tissue damage after induction of acute pancreatitis and to attenuate the extrapancreatic complications, suggesting that superoxide dismutase[35], polyethylene glycol-linked superoxide dismutase[38], allopurinol[11], CV 3611 (a synthetic ascorbic acid derivative)[10] and N-acetylcysteine[9,13], may play their role in attenuating the extrapancreatic complications. N-acetylcysteine is converted to metabolites capable of stimulating glutathione synthesis[12] and is an important antioxidant and essential cofactor for antioxi-

Table 5 Serum and urine amylase activity before ERCP, after 8 and 24 h in control and ACC groups (mean ± SD)

Serum and urine amylase activity levels		Control group (%)	ACC group (%)	*P*
before ERCP	serum	62.1 ± 59.7	79.0 ± 79.4	NS
	urine	272.9 ± 320.5	268.1 ± 355.2	NS
8 h after ERCP	serum	324.6 ± 487.1	270.1 ± 484.7	NS
	urine	596.3 ± 1108.3	775.9 ± 1500.4	NS
24 h after ERCP	serum	268.6 ± 590.9	183.56 ± 252.1	NS
	urine	1324.8 ± 2763.9	1033.7 ± 2499.6	NS

Table 6 Summary of the results of forward selection multiple logistic-regression analysis with development of post-ERCP acute pancreatitis as the outcome variable

Variable[1]	Odds ratio	95% CI	*P*
Precut (no precut *vs* precut)	0.108	0.026-0.456	0.003
Sex (F *vs* M)	7.432	0.841-65.689	0.071

[1] Other variables that were examined but did not enter the model including N-acetylcysteine treatment, multiple cannulations, bile duct diameter < 8 mm, injection of contrast into pancreatic duct, failed procedure and age.

dant enzymes, and is depleted in AP[39].

Nuclear factor-kappaB (NF-κB), an oxidant-sensitive transcription factor, may regulate the induction of cytokine gene expression, which in turn regulates inflammatory response[13]. NF-κB activation and cytokine production in pancreatic acinar cells are suppressed by N-acetylcysteine[13,40]. It was reported that of ACC use in patients suffering from acute pancreatitis and multiorgan failure can improve their clinical status[15].

The occurrence of pancreatic damage after ERCP may be due to extraductal leakage of the pancreatic juice present in the ducts, rupture of acini or alterations of the acinar cells. Such functional alterations cause leak of pancreatic enzymes into the interstitium and then into the blood, consequently leading to hyperamylasemia and hyperamylasuria. In our study, ACC treatment had no influence on post-ERCP serum and urine amylase activities, suggesting that ACC does not ameliorate pathophysiologic mechanisms operating post-ERCP, leading to leak of pancreatic enzymes.

Our results are consistent with those obtained by Katsinelos *et al*[16]. There are however some differences between the present study and that of Katsinelos and colleagues[16]. We used a lower dose of N-acetylcysteine, which is similar to that used for the prevention of nephrotoxicity by contrast agents[41]. Although in AP experimetal models doses are used as high as 1000 mg/kg[9], there is evidence that high doses might actually have deleterious effects on the course of AP by inducing apoptosis probably due to inhibiting NF-κB[42,43].

Although our study was underpowered, it should be noted that increasing sample size would probably not yield different results. We initially assumed 10% rate of post-ERCP pancreatitis, it would be 3% in the treatment group. Then the number of patients required for the study with a two-sided 5% significance test and a power of 80% was 194 per group. Interim analysis was performed after inclusion of 106 patients to determine if a larger sample might change findings. An effect size of 0.077 calculated from the power analysis indicated that a statistically significant difference did not occur even if the study was continued and enrolled preplanned number of patients. In fact it would be necessary to recruit at least 669 subjects in each group to demonstrate any statistical significance, a clearly untenable goal. In addition, N-acetylcysteine treatment had no statistically significant influence on serum amylase activity. Therefore a decision to terminate the study was made.

We also attempted to identify conditions predisposing patients to the development of AP post-ERCP. In the present study, precut papillotomy was significantly associated with increased risk of pancreatitis, suggesting that this factor reflects the technical difficulty of the procedure.

In conclusion, N-acetylcysteine fails to demonstrate any significant preventive effect on post-ERCP pancreatitis, as well as on serum and urine amylase activity. Pancreatic injury is related to endoscopic maneuvers performed to obtain biliary access, rather than to the patient-related factors. Hence, a therapeutic agent with significant prophylactic effect on post-ERCP pancreatitis is still needed and it is necessary to perform more studies[44].

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