

THE COMPARISON OF THE EFFECT OF SOMATOSTATIN AND SMS 201-995 ON ENZYME CHANGE FOLLOWING ENDOSCOPIC RETROGRADE CHOLANGIOPANCREOTOGRAPHY

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SUMMARY :

Purpose : The aim of this study was to compare the preventive effects of SMS 201-995 and somatostatin in endoscopic retrograde cholangiopancreatography (ERCP)-induced hyperamylasemia. **Method:** Ninety patients who underwent ERCP were included in our study and were divided in to three equal groups. Group 1 was treated with SMS 201-995 and the second group was treated with somatostatin. The control group (group 3) received only intravenous saline. Serial blood samples were withdrawn pre-ERCP and at timed intervals after ERCP (4th hour, 24th hour) for determination of blood amylase levels. **Results:** Before ERCP, the serum levels of amylase were significantly higher in the control group than in both treatment groups, although they remained within the range of normal values in all groups. There were no significant statistical differences between the two treatment groups ($p>0.05$). At 4 hours and 24 hours after ERCP, the mean serum amylase levels were significantly lower in the somatostatin group, compared to the other groups at both times. **Conclusion :** According to our results, somatostatin was more potent than its synthetic long-acting analogue in inhibiting ERCP-induced hyperamylasemia.

Key Words: Somatostatin, SMS 201-995, ERCP

INTRODUCTION

The incidence of ERCP-induced hyperamylasemia is 40-75% and acute pancreatitis is 0.7-7.4%. (1,2) ERCP-induced pancreatitis is a common clinical problem, but its treatment remains nonspecific and primarily supportive. The suppression of pancreatic exocrine function has long been accepted as a cornerstone in the treatment of acute pancreatitis because pancreatic stimulation in the patient recovering from acute pancreatitis often causes acute exacerbation of the disease. Both somatostatin and its analogue SMS 201-995 suppress pancreatic exocrine and endocrine secretions (3,4). The aim of this study

was to investigate the difference between somatostatin and SMS 201-995 in preventing ERCP-induced hyperamylasemia and/or pancreatitis.

PATIENTS AND METHODS

The study was prospective and randomised. Two hundred and forty-nine patients were randomised but 159 of these were excluded because of *i*) the need for endoscopic sphincterotomy, implantation of papillary stent, or basket appliance *ii*) filling of only the bile ducts or incomplete filling of the pancreatic duct. The inclusion criterion for 90 patients was the cannulation of papilla without any

other manipulations (papillotomy, basket appliance etc.) for the diagnosis. Included were the patients meeting the following criteria: *i*- the total serum bilirubin level exceeding 40mol/L and/or *ii*- the serum alkaline phosphatase level above 350 IU/L in relation to serum gammaglutamyl transpeptidase level above 100 IU/L, or liver specific alkaline phosphatase elevated *iii*- with or without revealing any biliary stones, a dilated common bile duct (6 mm) image determined by ultrasonography. The causes of exclusion were endoscopic sphincterotomy in 101 patients, incomplete or overfilling of the pancreatic duct in 25 patients, only bile duct opacification in 19 patients (failure of pancreatography), basket appliance to the duct stones in 4 patients and implantation of papillary polyvinyl stents in 5 patients. As a result, 90 patients who underwent ERCP were included in our study and were divided into three equal groups. In the control group, 30 patients 17 female, 13 male, mean age 50.28.8 yr received intravenous (i.v) infusion of 250cc isotonic sodium chloride for 4 h. The octreotide group 11 female, 19 male, mean age 465.8 yr was treated with 3x100g/day of SMS 201-995 (Sandostatin, Sandoz, Switzerland) subcutaneously on the ERCP day. The somatostatin group 19 female, 11 male, mean age 44.76.7 yr received a 3.5g/kg iv bolus of somatostatin (Somatostatin UCB, Pharma, Belgium) at the start of ERCP and then, 250g iv infusion of somatostatin for 4 h. All patients gave written informed consent before this study was performed. After an overnight fast, premedication consisted of pharyngeal anaesthesia with xylocaine spray and the patients were sedated with 10 mg midazolam (Dormicum, Roche, Switzerland). Duodenal relaxation was achieved with 40 mg hyoscine-n-butylbromide (Buscopan, Eczacıbaşı, Turkey) intravenously. An Olympus JF-IT side-viewing duodenoscope was used with an Olympus light source. In all patients, the same contrast medium (non-ionic Iohexol 300 mg/dl, 672 mOsm/kgH₂O) was used. The amount of contrast medium injected into the pancreatic duct was registered in all cases. The endoscopist was blinded to the study groups. Serial blood samples were withdrawn pre-ERCP and at timed intervals after ERCP (4 h, 24 h) for the measurement of serum levels of pancreatic isoamylase. In this study, all blood samples were evaluated on the same day. Pancreatic isoamylase was measured by the

amyloclastique technique of Boehringer-Meinheim (Germany). Oral intake was prohibited in all patients for the same period of time. For the statistical parametric analysis, one way ANOVA, Tukey honestly significant difference tests were used, and we analysed nonparametric values with Kruskal Wallis H and Mann Whitney- U tests in SPSS for Windows 6.0 (p is significant for 0.05).

RESULTS

The radiological diagnoses in the octreotide group were normal pancreatic duct in 26 patients and alterations indicating chronic pancreatitis in 4 patients. In the somatostatin group, the pancreatic duct was normal in 27 patients and signs of chronic pancreatitis existed in 3 patients. The diagnoses of the control group were normal in 29 patients and chronic pancreatitis in 1 patient. There were no significant side effects or remarkable differences in duodenal motility in the study groups. The number of cannulations was similar in all groups with a median of two cannulations. The amount of contrast medium injected into the pancreatic duct did not differ statistically between the three groups 4.40.9 ml (somatostatin), 4.51.0 ml (control), 4.71.1 ml (SMS 201-995) (p>0.05). The average time of the ERCP was 63.3 min (SD28.0) in the control group versus 61.8 min (SD27.0) in the octreotide group, 62.6 min (SD26.8) in the somatostatin group (p>0.05). Serum amylase levels rose significantly immediately after ERCP in all groups. No patients in this study developed clinical evidence of acute pancreatitis after ERCP. Before ERCP, there were significant differences in the serum levels of pancreatic isoamylase between the control group and the others (p control-octreotide= 0.018, p control-somatostatin= 0.0012) (Table 1), but there existed no significant statistical difference between the treatment groups (p = 0.086). This significance may be caused by the fact that most of the patients who had distal common bile duct stones were incidentally in the control group (in the control group 14/30, in the SMS 201-995 group 8/30, in the somatostatin group 7/30).

Serum pancreatic isoamylase peaked in controls at 4 h (p control-octreotide= 0.001, p control-somatostatin= 0.001) and decreased slowly without returning to pre-ERCP values at 24 h (p control-octreotide= 0.001, p control-somatostatin=0.001). Meanwhile, it peaked in both the somatostatin and octreotide groups at 4 h after

	Pre-ERCP	4 hour	24 hour
Control	84.0 ± 19.2*	178.6 ± 44.3	140.6 ± 23.2
SMS 201-995	69.5 ± 7.0	110.5 ± 19.8	99.1 ± 11.0≠
Somatostatin	65.3 ± 5.4	90.9 ± 23.0*	83.2 ± 5.8*

* : Significantly less than the other two groups ($p < 0.05$)

≠ : Significantly less than the control group ($p < 0.05$)

Table 1 : Mean values of isoamylase of the study groups (normal range: 25-125 U/l).

ERCP. Though the peak serum pancreatic isoamylase level in octreotide group at 4 h was lower than that of the control group, it was statistically higher than that of the somatostatin group (p control-octreotide= 0.001, p octreotide-somatostatin= 0.027).

After ERCP, the mean serum pancreatic isoamylase levels were significantly lower in the somatostatin group compared with those of the other two groups at 4 h. At 24 h, there was also a statistical difference between the SMS 201-995 and somatostatin groups, and both treatment groups possessed significantly lower pancreatic isoamylase levels, compared with the control group (p control-octreotide= 0.001, p octreotide-somatostatin= 0.027, p control-somatostatin= 0.001).

After ERCP, the serum amylase increased to pathological levels in 21 patients in the control group, in 10 patients in the SMS 201-995 group, and in 1 patient in the somatostatin group. The changes in serum amylase levels in the three groups before ERCP and 4 h and 24 h after ERCP are shown in Figure 1. The mean serum amylase levels 4 h and 24 h after ERCP were significantly lower in the somatostatin group as compared to the octreotide and control groups.

DISCUSSION

Cicero et al. showed that the peak level of serum pancreatic amylase after ERCP appeared at 4 h and this level decreased in 24 h. Therefore, we only measured the 4 and 24 h pancreatic isoamylase levels in our patients (5).

The tetradecapeptide somatostatin has been reported to reduce both basal and secretin-stimulated pancreatic exocrine secretion in man (6-9). Therefore, it has been used in the treatment of acute pancreatitis (10-14). On the basis of these findings, it would seem logical to administer somatostatin during or after ERCP in order to

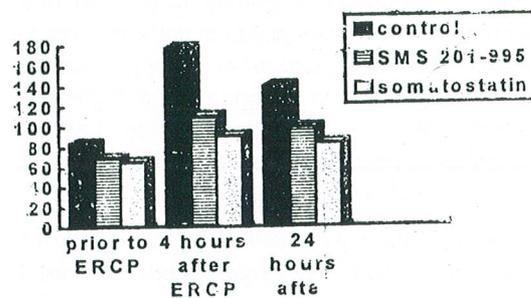


Fig - 1 : Serum amylase levels of the study groups.

reduce the incidence of hyperamylasemia and/or pancreatitis. The enzyme changes after ERCP are similar to those that are noted in acute pancreatitis (15). The use of somatostatin or its long-acting analogue SMS 201-995 has been reported to reduce the post-ERCP rise in serum amylase levels (4, 15-21). In the literature, considerable controversy exists about the effect of both somatostatin and SMS 201-995 in preventing enzyme changes and/or pancreatitis after ERCP.

However, Bordos (22) and Guelrub (23) reported that the use of somatostatin during ERCP could prevent pancreatic injury and pancreatitis. Although some studies suggested that somatostatin did not influence hyperamylasemia induced by ERCP (24, 25), somatostatin has never been claimed to increase the risk of pancreatitis after ERCP.

SMS 201-995 is a long acting synthetic analogue of somatostatin. It has been reported to reduce post-ERCP rise in serum amylase levels (7, 11, 12). Another study demonstrated that octreotide reduced plasma amylase concentration

by 39 % in rats with cerulein- induced acute pancreatitis (26). In our study, both SMS 201-995 and somatostatin decreased 24 h post-ERCP plasma amylase concentration by approximately 10 % compared with 4 h post-ERCP. Although SMS 201-995 is a long-acting analogue, its long-term effect was not more profound than that of somatostatin. On the contrary, Sternlieb et al. reported that octreotide increased the risk of acute pancreatitis in ERCP patients (27). Other authors have also reported high incidences of post-ERCP pancreatitis in patients treated with SMS 201-995, because SMS 201-995 was shown to increase both the basal Oddi sphincter tone and the frequency of phasic contractions (12, 28-30). This increased sphincter pressure might prolong the presence of a hyper/hypotonic contrast medium in the pancreatic duct and lead to increased incidence of pancreatitis (31). Also, Conway et al. reported that high-dose octreotide decreased pancreatic blood flow, an effect that is potentially detrimental in rats with coexisting acute pancreatitis (32).

In our study, pancreatic amylase levels of somatostatin group were significantly decreased compared to the other two groups, 4 h and 24 h after ERCP. It seems, therefore, prophylactic somatostatin may slow the immediate increase in serum amylase following ERCP. SMS 201-995 also proved to be effective in preventing ERCP-induced hyperamylasemia and no clinical side effects were noted. Nevertheless, the preventive effect of somatostatin was more profound than that of SMS 201-995.

In conclusion, our study suggests that utilizing somatostatin in the setting of diagnostic endoscopic cholangiopancreatography has a more potent effect than SMS 201-995 for the prophylaxis of ERCP-induced hyperamylasemia.

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