Does the somatostatin analogue octreotide protect against ERCP induced pancreatitis?

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Abstract

This study evaluates the effect of the long acting somatostatin analogue octreotide on biochemical and clinical parameters of endoscopic retrograde cholangiopancreatography (ERCP) induced pancreatitis. Altogether 245 patients were randomised to receive either octreotide or isotonic saline. Octreotide (100 µg) was administered intravenously five minutes before ERCP and subcutaneously 45 minutes after ERCP. There were no significant differences in the median serum amylase and lipase activities at baseline, eight, and 24 hours after ERCP. Five patients (2%) developed clinical pancreatitis – three in the octreotide and two in the placebo groups. Excluding patients who developed pancreatitis, 43 (18%) developed abdominal pain after ERCP – 21 in the octreotide and 23 in the placebo groups. There were no significant differences in the median serum amylase and lipase values between the treatment groups. None of the 52 patients who had therapeutic interventions developed pancreatitis. This study suggests that octreotide may not protect against ERCP induced pancreatitis.

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Endoscopic retrograde cholangiopancreatography (ERCP) is now well established in the diagnosis and treatment of biliary and pancreatic disorders. Although the procedure is generally considered to be safe, complications related to cannulation, contrast injection, and sphincterotomy may occur, and include cholangitis, haemorrhage, perforation, and pancreatitis.^{1,2} Pancreatitis is the most common of these complications. Clinically severe pancreatitis is reported to occur in 1-7% of patients,¹⁻⁵ while an asymptomatic increase in pancreatic enzyme activities may occur in up to 70%.⁶

Various gastrointestinal hormones such as glucagon and calcitonin have been investigated in studies on the prevention of ERCP induced pancreatitis.⁷⁻⁹ Somatostatin and a long acting analogue, octreotide, have received particular attention recently. Both are potent known inhibitors of pancreatic secretion. Several studies in healthy volunteers have shown inhibition of baseline and stimulated exocrine pancreatic secretion.¹⁰⁻¹² Four animal studies of experimentally induced acute pancreatitis have shown an improvement in the pancreatic enzyme response after the infusion of cyclic somatostatin or octreotide.¹³⁻¹⁶ Three of the four studies showed a concomitant improvement in histology.^{13 15 16} In three studies, pancreatitis was induced chemically,¹⁴⁻¹⁶ and in one by ligation of the pancreatic duct¹³ – a model that is probably

more analogous to ERCP induced pancreatitis. In the latter study, somatostatin and octreotide improved the enzyme response, histology, and survival.

Several clinical studies evaluating the effect of somatostatin or octreotide on ERCP induced pancreatic reactions have been published¹⁷⁻²⁶ but their results have been conflicting. We undertook a randomised, controlled study in 245 patients to evaluate the effect of the somatostatin analogue octreotide on biochemical and clinical parameters of ERCP induced pancreatitis.

Methods

This study was designed as a controlled clinical trial, incorporating a double blind placebo control. Exclusion criteria were as follows: (1) age under 18 or above 85 years; (2) pregnancy; (3) albuminuria greater than 500 mg per 24 hours; (4) acute myocardial infarction in the three months before the study; (5) a history of asthma or allergy to drugs. Informed consent was obtained from all the patients. Patients were randomly allocated to receive either the long acting somatostatin analogue octreotide (n=121) or isotonic saline intravenously as a placebo (n=124). Octreotide was given five minutes before ERCP as an intravenous bolus injection of 100 µg and immediately after ERCP as a subcutaneous injection of 100 µg.

Before ERCP, all patients received premedication consisting of hyoscine-n-butyl bromide (Buscopan) with pethidine (Meperidine) and/or diazepam (Valium) intravenously titrated to age and tolerance. Antibiotics (cefotetan and metronidazole) were given before and after ERCP in patients with cholangitis. All patients were in hospital and confined to bed for at least 24 hours after ERCP. Fasting was maintained for a minimum of six hours.

ERCP was performed with the Olympus JFIT10 or TJF10 endoscopes. Contrast medium (65% angiografin in normal saline) was injected manually in a controlled, titrated fashion under fluoroscopic control. When indicated, sphincterotomy was performed using a standard Erlangen type sphincterotome. Endoprosthesis placement was performed in the conventional manner using a plastic prosthesis for the bile and pancreatic ducts.

Selective cannulation of the biliary and/or pancreatic duct was attempted in all patients. Ductal cannulation was rated as 'easy' if cannulation could be achieved immediately, and as 'difficult' if it required repeated attempts leading to obvious trauma to the papilla.

Assessment of the following clinical parameters was performed before ERCP, immediately after ERCP, and eight and 24 hours after

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TABLE I Clinical data of treatment groups

	Octreotide	Placebo
No of patients	121	124
Mean age (years)	58	61
Sex M/F	65/56	63/60
Indication for ERCP:		
Chronic abdominal pain	54	51
Suspected pancreatic carcinoma	12	16
Pancreatitis	9	1
Pancreatic cyst	1	1
RUQ pain with abnormal LFTs	16	27
Cholestasis/jaundice	18	10
Chronic alcoholism	16	11
Other	1	2

ERCP=endoscopic retrograde cholangiopancreatography;
RUQ=right upper quadrant; LFTs=liver function tests.

TABLE II Endoscopic retrograde cholangiopancreatography (ERCP) results

	Octreotide group	Placebo group
Failed ERCP	8	1
ERP only	68	83
ERC only	25	23
ERC only	20	17
Volume of contrast media injected (mean (cc))	44	45
Repeated pancreatic duct injections	45	34
Pancreatic duct overfilling	22	16
Papillary 'pre-cut'	1	2
Sphincterotomy	15	24*
Endoprosthesis placement:		
Biliary	10	2
Pancreatic	0	1

*Two pancreatic sphincterotomies.

ERCP: (1) presence and character of abdominal pain; (2) requirement for analgesics; and (3) body temperature. Serum amylase and lipase activities were determined in serial blood samples taken before (baseline) and eight and 24 hours after ERCP. Hyperamylasaemia and hyperlipasaemia were defined as increases above the upper limits of normal, which were 52 IU/l and 200 IU/l respectively, before January 11, 1989, and 10 IU/l and 208 IU/l, respectively, after January 11, 1989. ERCP associated pancreatitis was defined by clinical features consistent with acute pancreatitis beginning after ERCP and lasting for at least 24 hours, associated with an increase in serum amylase and/or lipase greater than three times the upper limit of normal. The white blood cell count was determined immediately before and at the end of the study; leukocytosis was defined as a white cell count greater than 10 000 cells/mm³.

Figure 1: Numbers of patients in the octreotide treated and placebo groups with easy and difficult cannulations.

STATISTICAL ANALYSIS

Comparison of quantitative data between the two groups was performed by Student's *t* test when normal distribution of the data could be assumed, and by Mann-Whitney U test when distribution could not be assumed to be normal (serum and amylase values). Comparison of categorical data between the two groups was performed with the χ^2 test (with Yates's correction when necessary) or with Fischer's exact test. A *p* value less than 0.05 was the accepted level of significance.

Results

Comparison of age, sex, and indication for ERCP showed no significant differences between the octreotide and placebo groups (Table I).

ERCP results are shown in Table II. Cannulation of the papilla failed in nine patients. The pancreatic duct was filled in 199 patients (84%). The octreotide and placebo groups were similar in terms of pancreatic duct filling, number of pancreatic duct injections, volume of contrast media injected, and pancreatic duct overfilling producing acinar opacification. Therapeutic ERCP procedures (39 sphincterotomies and 13 endoprosthesis placements) were performed in 18% of patients.

The numbers of patients in the octreotide and placebo groups with 'easy' and 'difficult' cannulations of the bile and pancreatic ducts is given in Figure 1.

The diagnostic findings at ERCP are detailed in Table III.

Five patients (2%) developed ERCP associated pancreatitis – three in the octreotide and two in the placebo groups. Table IV details the ERCP and clinical data for these patients. All had undergone injection of the pancreatic duct, three had repeat injections, and two had overfilling resulting in acinar opacification. Two patients had duct pathology seen on pancreatography. None had a therapeutic intervention. The clinical course was uncomplicated in all patients.

Comparison of the median serum amylase and lipase activities at baseline and at eight and 24 hours after ERCP in the octreotide and placebo groups showed no significant differences between the two treatment groups (Fig 2).

Excluding those patients who developed pancreatitis, 43 (18%) developed non-specific post ERCP abdominal pain – 21 in the octreotide and

TABLE III Endoscopic retrograde cholangiopancreatography-diagnostic findings

Findings	Octreotide group	Placebo group
Normal	62	60
Biliary pathology:		
CBD stones	8	13
Malignant stricture	8	6
Papillary stenosis	0	2
Sump syndrome	0	2
Dilated CBD	11	10
Other	1	
Pancreatic pathology:		
Chronic pancreatitis	9	16
Pancreas divisum	8	6
Dilated pancreatic duct	3	2
Pancreatic carcinoma	4	7

CBD=common bile duct.

TABLE IV Clinical characteristics of patients who developed pancreatitis

No	Treatment	Sex	Age (yrs)	ERCP diagnosis	ERP	PD overfilling	Repeated PD injections	Pain duration
1	OCT	F	58	Dilated PD	Yes	Yes	Yes	25 Days
2	OCT	M	56	Chronic pancreatitis	Yes	No	No	24 Hours
3	OCT	F	63	Normal	Yes	No	No	24 Hours
4	PLAC	F	61	Dilated CBD	Yes	No	No	3 Days
5	PLAC	M	55	Normal	Yes	Yes	Yes	24 Hours

OCT=octreotide; PLAC=placebo; PD=pancreatic duct; CBD=common bile duct; ERP=endoscopic retrograde pancreatography.

23 in the placebo group. Comparing the two treatment groups, there were no significant differences in the median serum amylase and lipase activities at baseline and at eight and 24 hours (Fig 2). However, comparing the subgroup of patients that developed abdominal pain with the subgroup that did not, the former had significantly higher median serum amylase and lipase values at both eight and 24 hours (Fig 3).

No significant side effects attributable to octreotide were observed during the study.

Discussion

Our study of 245 patients randomised to receive octreotide or placebo failed to show an effect of octreotide on the biochemical and clinical parameters of ERCP induced pancreatitis. There was no significant difference in median serum amylase or lipase activities, and the occurrence of abdominal pain and clinical pancreatitis was similarly represented in the two treatment groups.

Previous controlled studies evaluating the effect of somatostatin or octreotide on biochemical, clinical, and morphological markers of pancreatitis have shown mixed results.¹⁷⁻²⁶ All studies were small in sample size. Comparison is difficult because of variability of drug administration (route, dosage, and schedule), patient composition, and type of ERCP procedures performed.

Two studies by Tulassay *et al* showed that prophylactic administration of somatostatin or octreotide reduced high pancreatic enzyme activities after ERCP.^{17,18} In a non-randomised study, 20 patients who received cyclic somato-

statin had a fourfold reduction in serum amylase values compared with 35 controls. A total of 875 µg of somatostatin were administered before and after ERCP over a 150 minute period.¹⁷ In a randomised double blind study, 29 patients who received octreotide in a dose of 0.1 mg subcutaneously given 45 minutes before ERCP had a significantly smaller increase in pancreatic enzyme activities compared with 34 control subjects.¹⁸ An analysis of clinical parameters was not performed in either study.

A randomised double blind study of 38 patients by Cicero *et al* showed a significant reduction in pain intensity and maximum increase in pancreatic enzymes in patients that received 1000 µg of cyclic somatostatin before and four hours after ERCP compared with control subjects.¹⁹ Morphological evaluation of the pancreas with echography in 33 patients showed that those treated with somatostatin had a significantly greater increase in the antero-posterior diameter of the pancreas after injection. In a similarly designed study of 33 patients, Bordas *et al* showed a significant reduction in abdominal pain and pancreatic enzyme increase in patients who received a bolus injection of natural somatostatin (4 µg/kg body weight) before ERCP.²⁰

In a randomised study of 16 patients with idiopathic recurrent pancreatitis who were undergoing hydrostatic balloon dilation of the pancreatic duct sphincter, somatostatin given intravenously at a dose of 250 µg/hour one hour before and 12 hours after dilatation reduced the incidence and severity of acute pancreatitis compared with placebo.²¹ In this study, 43% of patients developed acute pancreatitis.

In contrast, several controlled studies have failed to show a protective effect of somatostatin or octreotide in ERCP induced pancreatitis.²²⁻²⁶ In a study of 56 patients randomised to somatostatin or placebo, somatostatin, administered in a dose of 250 µg/hour after contrast media emptying of the pancreatic duct, did not reduce hyperamylasaemia or pancreatitis like pain.²² A smaller study of 20 patients showed no difference between the median rise in serum amylase values between the somatostatin (250 µg/hour given before ERCP and continued for 24 hours) and placebo groups.²³ In a study of 54 patients undergoing endoscopic sphincterotomy, the continuous infusion of cyclic somatostatin in a dose of 250 µg/hour over 26 hours beginning two hours before ERCP did not significantly reduce pancreatic enzyme rise compared with placebo.²⁴ A study of 26 patients who received somatostatin in a dose of 250 µg/hour over 24 hours did not show significant reduction in amylase activities compared with historical controls.²⁵

The preliminary results of a multicentre study suggest that octreotide may increase the incidence of ERCP induced pancreatitis.²⁶ In a randomised study of 84 patients, octreotide, given in a dose of 100 µg intravenously immediately before ERCP and subcutaneously 45 minutes later, significantly increased the incidence of pancreatitis from 11% (control group) to 35% (octreotide group).

Controlled clinical studies evaluating somatostatin in acute pancreatitis have not shown

Figure 2: Median serum amylase and lipase activities at baseline and at eight and 24 hours after ERCP in the octreotide treated and placebo groups.

Figure 3: Median serum amylase and lipase activities at baseline and at eight and 24 hours after ERCP in the subgroup of patients with post ERCP abdominal pain.

statistically significant advantages in terms of complications and mortality, although trends toward fewer complications²⁷ and better pain relief²⁸ were observed.

Because of the low incidence of clinical pancreatitis after ERCP, investigators have studied the effect of somatostatin or octreotide on ERCP associated abdominal pain as a surrogate marker of pancreatitis. The incidence of abdominal pain after ERCP, excluding cases of diagnosed pancreatitis, was 18% in our study. We found that patients who developed abdominal pain had significantly higher median serum amylase and lipase values than asymptomatic patients, a finding that tends to validate abdominal pain as a marker of 'subclinical' pancreatitis. Comparison of the median serum amylase and lipase activities at baseline and eight and 24 hours after ERCP between the octreotide and placebo groups showed no significant differences.

Risk factors for ERCP induced pancreatitis have been identified and include repeated pancreatic duct injections, overfilling of the pancreatic duct, and the presence of a diseased ductal system.^{2,5,29} In our study, all patients who developed pancreatitis had injection of the pancreatic duct, three had repeat injections, two had overfilling resulting in acinar opacification, and two had ductal pathology on pancreatography. La Farla *et al.*⁴ found that endoscopic sphincterotomy significantly increased the incidence of pancreatitis after ERCP, however, none of the patients who underwent sphincterotomy in our study developed pancreatitis.

Eight of nine cases of failed papillary cannulation were in the octreotide group, and patients in the octreotide group tended to have fewer 'easy' as well as more 'difficult' cannulations of the bile and pancreatic ducts (Fig 1). This raises the question of whether octreotide increases sphincter of Oddi pressure, rendering ductal cannulation more difficult. The effect of somatostatin on the human sphincter of Oddi has not been established. We studied the effect of octreotide administered in a dose of 50 µg on the sphincter of Oddi using endoscopic manometry in seven patients and found that this hormone increased basal pressure and the frequency of phasic wave contractions appreciably.³⁰ In the

prairie dog and rabbit, somatostatin has been shown to inhibit sphincter of Oddi motility,^{31,32} but this effect may be species specific. The gastrointestinal hormone cholecystokinin has been shown to have an opposite effect on the human sphincter of Oddi compared with that of the rabbit and prairie dog.³²⁻³⁵

Excitatory effects of somatostatin or octreotide on the sphincter of Oddi may impair biliary and pancreatic duct outflow. Such a mechanism is indirectly supported by human studies showing that cholecystokinin, a hormone with antagonistic properties to somatostatin on the sphincter of Oddi,^{32,37} increases bile flow into the duodenum.^{35,37} One study of experimental pancreatography in anaesthetised piglets showed that somatostatin significantly delayed ductal emptying of contrast media compared with control animals.²²

Based on the above considerations, it is possible that a pancreatic protective effect of octreotide as shown in experimental models of pancreatitis¹³⁻¹⁶ may be clinically offset by an increase of sphincter of Oddi pressure leading to pancreatic duct outflow obstruction. More difficult cannulation at ERCP resulting in papillary oedema may contribute to outflow obstruction. The administration of somatostatin or octreotide after complete emptying of the contrast media filled pancreatic duct may produce different results.

Despite the large number of patients recruited for this study, from a purely statistical standpoint a significantly larger number of subjects would be required to eliminate a type II error in a negative study due to the low incidence of ERCP induced clinical pancreatitis. Such a study would clearly be a major undertaking, and might be difficult to justify in view of mixed results in smaller studies. Studies evaluating somatostatin or octreotide in therapeutic ERCP procedures associated with a higher incidence of pancreatitis, such as manipulation of the pancreatic duct sphincter with hydrostatic balloon dilators,²¹ would be better suited for future studies.

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