

## The Effect of Short-Term Octreotide Administration on the Histologic Structure of Stomach, Duodenum, Jejunum, Colon, Liver and Gallbladder in an Experimental Pancreatitis Model

ATILLA SORAN, MÜKERREM CETE and CAVIT ÇÖL

*The First Department of Surgery, Ankara Numune Teaching Hospital, Ankara 06100, Turkey*

SORAN, A., CETE, M. and ÇÖL, C. *The Effect of Short-Term Octreotide Administration on the Histologic Structure of Stomach, Duodenum, Jejunum, Colon, Liver and Gallbladder in an Experimental Pancreatitis Model.* Tohoku J. Exp. Med., 1998, **185** (2), 101-106 — It is known that long-term administration of octreotide leads to changes in the histology of intraabdominal organs and plasma biochemical values. The purpose of the present study was to evaluate the histological effect of short-term octreotide administration on digestive organs in the experimentally induced pancreatitis by ligating pancreatic duct. The sham operation was performed on 20 rabbits in Groups 1 and 2. Acute pancreatitis was induced by pancreatic duct ligation in 20 rabbits in Groups 3 and 4. Octreotide was administered subcutaneously to the rabbits in Groups 2 and 4 at a dosage of 10  $\mu\text{g}/\text{kg}/\text{day}$  for 7 days. The animals were sacrificed at the end of day 7, blood and tissue samples were collected. There was no histological changes in the stomach, duodenum, gallbladder, or small and large intestines of those group which received octreotide, while hepatic bile duct proliferation, bile duct epithelium proliferation, periportal inflammation and venous stasis were observed in liver histology. In conclusion, one-week octreotide administration in this experimental acute pancreatitis model was not associated with pathologic changes in digestive organs except liver. ——— octreotide; acute pancreatitis; histological changes of digestive organs © 1998 Tohoku University Medical Press

Treatment and prognosis of acute pancreatitis remain to be a common problem. Although several treatment protocols have been suggested, their benefit is still limited. While the medications used to treat acute pancreatitis have therapeutical efficacy, they also may cause damage in other organs. Recent extensive experimental and clinical trials have revealed the importance of

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Address for reprints: Atilla Soran, M.D., University of Pittsburgh Medical Center, 446 S. Aiken Ave. Apt 4. Pittsburgh, PA 15232, USA.

e-mail: asoran+@pitt.edu

somatostatin among the therapeutical alternatives in acute pancreatitis (Choi et al. 1989). Although somatostatin and its synthetic analogues have been extensively used in clinical practice, there is no histological study in the literature demonstrating the effect of short-term somatostatin administration on other gastrointestinal organs in experimental models of acute pancreatitis. Gastric cellular damage and hepatitis have been previously reported during long-term treatment of acromegaly (Arosio et al. 1988; Plockinger et al. 1994). We investigated the effect of short-term administration octreotide, an analogue of somatostatin on the histologic structures of the liver, stomach, duodenum, small intestine, colon and gallbladder in an experimental model of pancreatitis induced by pancreatic duct ligation in rabbits.

#### MATERIALS AND METHODS

Median incisions were performed in 40 New Zealand rabbits of both sexes with a body-weight of 2500 to 3500 g. General anaesthesia was induced by administration of thiopentone sodium (20 mg/kg) into the ear vein. The sham operation (animals underwent laparotomy, and pancreatic duct palpated but not ligated) was performed on 20 rabbits in Groups 1 and 2. Acute pancreatitis was induced by pancreatic duct ligation in 20 rabbits in Groups 3 and 4. Octreotide (Sandostatin, Basel, Switzerland) was administered subcutaneously to the rabbits in Groups 2 and 4 at a dosage of 10  $\mu$ g/kg/day for 7 days (Eliakim et al. 1993; Morris et al. 1993). The animals were allowed water and standard food when they awoke. The animals were sacrificed at the end of day 7, blood and tissue samples were collected. Blood samples were centrifuged for later measurement of plasma amylase levels while tissue samples were fixed in a 10% formaldehyde solution. The tissue sections were stained with haematoxylin-eosin and examined by a pathologist who was unaware of the treatment. Pancreatic tissue samples were histologically scored (Murayama et al. 1991) according to the following scale: edema (0-1 points), neutrophil infiltration (0-4 points), acinar vacuolisation (0-2 points), and acinar necrosis (0-2 points). "SPSS for Windows V 5.01" was used in the statistical analysis and comparisons between the groups were made by using Fisher's exact test. Significance was accepted when  $p < 0.05$ .

#### RESULTS

There was no death during the experimental study. Plasma amylase values significantly increased after pancreatic duct ligation (Table 1). Histological pancreatic scores revealed acute pancreatitis development in Groups 3 and 4.

There were no pathological findings in the stomach, duodenum, gallbladder, or small and large intestines among all the groups (Groups 1, 2, 3, 4). We did not examine *Helicobacter pylori* in resected gastric specimens.

Hepatic bile duct proliferation, bile duct epithelium proliferation were seen in groups received octreotide, and periportal inflammation and portal venous

TABLE 1. *Plasma amylase levels and histology score of the pancreas*

Groups ( <i>n</i> )	Plasma Amylase (U/L)	Histology Score
1 (10)	402.66 ± 47.72	1 ± 0.0
2 (10)	434.40 ± 7.08	1.33 ± 0.88
3 (10)	2131.5 ± 384.9*	7.33 ± 2.38*
4 (10)	1688.2 ± 187.6**	4.66 ± 1.08**

Values are expressed as mean ± SEM

\* $p < 0.05$  group 1 vs. group 3

\*\* $p < 0.05$  group 2 vs. group 4

Group 1: sham operation

Group 2: sham operation, received 10 µg/kg/day dose of octreotide subcutaneously.

Group 3: Acute pancreatitis animals

Group 4: Acute pancreatitis animals received subcutaneously 10 µg/kg/day octreotide.

TABLE 2. *The effects of octreotide on hepatic histology in acute pancreatitis*

	Group 1 <i>n</i> = 10	Group 2 <i>n</i> = 10	Group 3 <i>n</i> = 10	Group 4 <i>n</i> = 10
Bile duct proliferation	0%	80%	0%	60%
Bile duct epithelium proliferation	0%	80%	0%	70%
Portal area inflammation	0%	80%	20%	100%
Bile stasis	0%	0%	0%	20%
Venous stasis	0%	80%	100%	100%

See the note to TABLE 1 for the Groups

stasis were also significantly increase in those rabbits receiving octreotide ( $p < 0.001$ ) (Table 2 and 3). Short-term octreotide administration did not cause significant bile stasis in control and pancreatitis groups ( $p > 0.05$ ). Vacuolisation of hepatocytes was observed in Groups 1 and 3, and atrophy was examined in Groups 2 and 4 after octreotide administration.

## DISCUSSION

Although somatostatin and its synthetic analogues have a place in treatment protocols of patients with acute pancreatitis, their effect(s) on other organs remain unknown. Long-term studies have shown a decrease in serum vitamin B<sub>12</sub> concentration, mild to severe chronic active gastritis, inflammation, damage to the glandular and superficial epithelium, mucosal atrophy and an increase in intestinal metaplasia, and a high prevalence of *Helicobacter pylori* in 10 patients with acromegaly who received octreotide for over 2 years (Plockinger et al. 1994). These findings may be due to a direct inhibitory effect of octreotide on intrinsic factor release, as well as hypochlorhydria resulting from inhibition of gastrin

TABLE 3. *The effects of octreotide and pancreatic duct ligation on hepatic histology in acute pancreatitis*

	Octreotide		Ligation	
	(-)	(+)	(-)	(+)
	<i>n</i> = 20	<i>n</i> = 20	<i>n</i> = 20	<i>n</i> = 20
Bile duct proliferation	0%	70%	40%	30%
Bile duct epithelium proliferation	0%	75%	40%	35%
Portal Area inflammation	10%	90%	40%	60%
Bile stasis	0%	10%	0%	10%
Venous stasis	50%	90%	40%	100%

Octreotide (-): Groups 1 and 3

Octreotide (+): Groups 2 and 4

Ligation (-): Groups 1 and 2

Ligation (+): Groups 3 and 4

release. Furthermore, a delay in gastric emptying and a decrease in antral motility due to octreotide appear to be significant factors for gastric pathology (Londong et al. 1989; Haruma et al. 1994). Somatostatin-14 (SMS-14) has been found to have beneficial effects in the treatment of ethanol-induced haemorrhagic gastric lesions (Kusterer et al. 1994). In our study no pathologic change was observed on histological examination of the stomach of 20 rabbits after 7 day administration of octreotide, and no *Helicobacter pylori* was detected in the sections. We consider that development of mucosal changes may require a longer duration of gastric irritation. Octreotide was administered only a week in the present study.

As a consequence of disturbed pancreatic exocrine release, duodenal contents with a low pH leads to hyperplasia in duodenal intramucosal D cells, resulting in increased duodenal somatostatin content (Gujarro and Arilla 1988). The villous atrophy, hyperplasia/hypertrophy in paneth cells, and increase in goblet cells and intermediate glandular cells in the duodenum seen 6-14 weeks after the ligation of pancreatic duct (Gujarro and Arilla 1988) might not occur following short-term administration. Therefore, the absence of histologic changes in the duodenum during the study period reveals that short-term administration of octreotide is not associated with these pathologic changes that are likely to occur.

Octreotide has been shown to decrease the bile flow by inhibition of exocrine secretion and caused a dose-related inhibition of secretin both on bile flow and on biliary output of bilirubin conjugates (Ricci and Fevery 1989; Gyr and Meier 1993). Notwithstanding Tracy et al. (1993) reported that somatostatin or its analogue, octreotide, in extrahepatic bile duct obstruction preserves hepatocyte volume and decreases DNA synthesis by hepatocytes, bile duct proliferation and periportal extracellular matrix deposition, we observed bile duct proliferation, bile duct epithelium proliferation and periportal inflammation in rabbits receiv-

ing octreotide irrespective of pancreatic duct ligation. It is well known that postcanalicullar biliary obstruction leads to bile duct epithelial cell proliferation and periportal fibrosis secondary to increased biliary tract duct pressure that results in an increase in DNA synthesis and hyperplasia (Tracy et al. 1993). In our experimental model pancreatic duct ligation provided us a homogenous, severe but not lethal pancreatic damage, and did not cause bile duct obstruction while we assessed the histology of the liver. We may suggest that in the absence of bile obstruction, 10  $\mu\text{g}/\text{kg}/\text{day}$  dose of octreotide causes the liver injury by decreasing of bile flow. Even if it was reported that a patient had idiosyncratic hepatitis induced by octreotide, this suggestion needs further dose-related experimental studies (Arosio et al. 1988).

Vacuolisation seen in hepatocytes may be considered as a normal morphologic structure, but it is known that certain medications used and inflammatory diseases may also present this histology (Lee 1994). Meanwhile, it has been emphasised that SMS-14 inhibits the early phase of hepatic regeneration and delay proliferation (Hashimoto et al. 1993). The predominance of atrophy in animals given octreotide (Groups 2 and 4) supports its effect on hepatic regeneration.

Somatostatin inhibits endogenous cholecystokinin release (Gujarro and Arilla 1988) and acetylcholine release from gallbladder myenteric plexus (Guillemin 1984). It also exerts an anti-choleretic effect decreasing fasting hepatic bile production (Magnusson et al. 1989), and with long-term administration of somatostatin, bile stasis as well as changes in the composition of bile lead to cholelithiasis (Lehy et al. 1979). Changes in bile lipid composition and presence of cholesterol crystals were detected in patients who received octreotide for 3 months (Koch et al. 1988). The increased incidence of cholelithiasis in pathologic conditions, which require long-term octreotide administration suggest that significant bile stasis, is dependent on the duration rather than the dose of treatment. The absence of pathological change in the gallbladder in spite of high doses of octreotide in the present study also confirms this conclusion.

Octreotide has been reported to inhibit the proliferation of intestinal epithelium and crypts, and cause a decrease in the number of goblet cells in the models of induced colitis (Eliakim et al. 1993). We did not observe any changes in gut histology, therefore, probably octreotide can only effect the damaged cells in gut.

In conclusion, octreotide did not affect the histology of digestive organs except liver in induced acute pancreatitis by pancreatic duct ligation while it reduced the serum amylase levels and improved the pancreas histology. The suggestion of octreotide induced liver injury needs further dose-related experimental studies.

#### References

- 1) Arosio, M., Bazzoni, N., Ambrosi, B. & Faglia, G. (1988) Acute hepatitis after treatment of acromegaly with octreotide. *Lancet*, **2**, 1498.

- 2) Choi, T.K., Mok, F., Zhan, W.H., Fan, S.T., Lai, E.C. & Wong, J. (1989) Somatostatin in the treatment of acute pancreatitis: A prospective randomised controlled trial. *Gut*, **30**, 223-227.
  - 3) Eliakim, R., Karmeli, F., Okon, E. & Rachmilewitz, D. (1993) Octerotide effectively decreases mucosal damage in experimental colitis. *Gut*, **34**, 264-269.
  - 4) Guillemin, R. (1984) Somatostatin. *N. Engl. J. Med.*, **309**, 1495-1501.
  - 5) Gujarro, L.G. & Arilla, E. (1988) Somatostatin levels and binding in duodenal mucosa of rabbits with ligation of pancreatic duct. *J. Endocrinol.*, **118**, 227-232.
  - 6) Gyr, K.E. & Meier, R. (1993) Pharmacodynamic effects of Sandostatin in the gastrointestinal tract. *Digestion*, **54**, 14-19.
  - 7) Haruma, K., Wiste, J.A. & Camilleri, M. (1994) Effect of octreotide on gastrointestinal pressure profiles in health and in functional and organic gastrointestinal disorders. *Gut*, **35**, 1064-1069.
  - 8) Hashimoto, M., Kothary, P.C. & Raper, S.E. (1993) The effects of transforming growth factor alpha and somatostatin on regenerating hepatocytes in the rat. *Regul. Pept.*, **44**, 49-59.
  - 9) Koch, T.R., Carney, J.A., Morris, V.A. & Go, V.L.W. (1988) Somatostatin in the idiopathic inflammatory bowel diseases. *Dis. Colon. Rectum.*, **31**, 198-203.
  - 10) Kusterer, K., Buchheit, K.H., Schade, A., Bruns, C., Nueberger, C., Engel, G. & Usadel, K.H. (1994) The Somatostatin analogue octreotide protects against ethanol-induced microcirculatory stasis and elevated vascular permeability in rat gastric mucosa. *Eur. J. Pharmacol.*, **259**, 265-271.
  - 11) Lee, R.G. (1994) Drug induced hepatic injury. In: *Diagnostic Liver Pathology*, edited by Mosby Year Book, Inc. Clarinda Company, USA, pp. 341-371.
  - 12) Lehy, T., Dubrasquet, M. & Bonfibs, S. (1979) Effect of somatostatin on normal and gastric stimulated cell proliferation in the gastric mucosa and intestinal mucosa of the rat. *Digestion*, **19**, 99-109.
  - 13) Londong, W., Angerer, M., Kutz, K., Landgraf, R. & Londong, V. (1989) Diminishing efficacy of octreotide (SMS 201-995) on gastric functions of healthy subjects during one week administration. *Gastroenterology*, **96**, 713-722.
  - 14) Magnusson, L., Einarsson, K., Angelin, B., Nyberg, B., Bergstrom, K. & Thulin, L. (1989) Effects of somatostatin on hepatic bile formation. *Gastroenterology*, **96**, 206-212.
  - 15) Morris, J.B., Guerrero, N.H., Furth, E.E. & Stellato, T.A. (1993) Somatostatin attenuates ischemic intestinal injury. *Am. J. Surg.*, **165**, 676-680.
  - 16) Murayama, K.M., Drew, J.B., Yokoo, H. & Joehl, R.J. (1991) Bile exclusion from gut exacerbates acute pancreatitis caused by pancreatic duct obstruction in rats. *Pancreas*, **6**, 175-181.
  - 17) Plockinger, U., Dienemann, D. & Quabbe, H.J. (1994) Gastrointestinal side effects of octreotide during long-term treatment of acromegaly. *J. Clin. Endocrinol. Metab.*, **71**, 1658-1662.
  - 18) Ricci, G.L. & Fevery, J. (1989) Somatostatin inhibits the effect of secretin on bile flow and on hepatic bilirubin transport in the rat. *Gut*, **30**, 1266-1269.
  - 19) Tracy, T.F., Tector, A.J., Kitchen, S. & Lagunoff, D. (1993) Somatostatin analogue (octreotide) inhibits duct epithelial cell proliferation and fibrosis after extrahepatic biliary obstruction. *Am. J. Pathol.*, **143**, 1574-1578.
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