Octreotide Decreases Biliary and Pancreatic Exocrine Function, and Induces Steatorrhea in Healthy Subjects

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A somatostatin analogue (SMS-201-995, hereinafter "octreotide") was s.c. administered to 5 healthy subjects under consecutive dripping of CCK-PZ (cholecystokinin-pancreozymin) and secretin (0.01 CHR U/kg/minutes), after inserting a Dreiling double tube into Treitz's ligament. Bile acid concentration, and bicarbonate and lipase excretions in duodenal juice were determined every 10 minutes up to 120 minutes and compared with controls. Moreover, octreotide (100 µg) was s.c. administered to 5 healthy subjects 30 minutes before meals for 7 days. Fecal fat and bile acid excretions before and after administration were determined. Bile acid concentration, and bicarbonate and lipase excretions in the octreotide group decreased to 1/3–1/4 that of controls. Bile acid concentration became 0 mM for 60 minutes. Fecal fat excretion increased; obvious steatorrhea occurred in 2 cases. Fecal bile acid excretion decreased to about 1/4. These results suggest that decreases in bile acid secretion should be considered, as well as pancreatic lipase and bicarbonate secretions, when fatty stool occurs after octreotide administration. (Internal Medicine 33: 593–596, 1994)

Key words: pancreozymin-secretin, biliary inhibition, inhibition of bicarbonate and lipase, somatostatin analogue, greasy stool

Introduction

Somatostatin is present in the stomach, small intestine, pancreas, etc. and exerts its physiological actions as a paracrine, endocrine, and neurotransmitter (1). Its principal effects on the target organ are the inhibition of gastrointestinal hormone functions (2–5), as well as the inhibition of the secretion of gastrointestinal hormones themselves, such as gastrin, cholecystokinin-pancreozymin (PZ), and secretin (6–8).

Somatostatinoma, which produces somatostatin, is very frequently complicated with cholelithiasis and steatorrhea (9). In contrast with endogenous somatostatin, which shows several minutes of biological half life, SMS-201-995 (Sandostatin®, hereinafter abbreviated as octreotide) is a somatostatin analogue, and has been developed and utilized as a therapeutic agent for endocrine gastrointestinal tumor (indicated for VIPoma, carcinoid, and gastrinoma in Japan). However, because it inhibits the functions of the above target organs (10) in addition to inhibiting the hormone secretion from the endocrine organs, adverse reactions develop in various gastrointestinal organs. In fact, when octreotide is used for a short period in patients with

carcinoid or for a long period in patients with endocrine gastrointestinal tumor, steatorrhea is aggravated (11, 12). When octreotide is used even in healthy subjects with 100 g of fat for a short period, it causes steatorrhea (13). It is reported (12) that the decrease (observed in one-third to one-fourth of healthy subjects) of lipase activity cannot cause the steatorrhea and that the administration of pancreatic extracts during octreotide administration offers no improvement in steatorrhea.

To clarify the mechanism of this steatorrhea, we investigated pancreatic bicarbonate secretion and bile acid concentration other than lipase secretion in healthy subjects treated with octreotide since all of these are necessary for fat digestion and absorption. Also, octreotide was administered before each meal to healthy subjects with a daily intake of 60 g fat and changes in the fecal fat and bile acid excretions were examined.

Subjects and Methods

The subjects were 8 healthy adult males (aged 20–30 years) who consented to participate in the test. The protocol was approved by the Institutional Human Investigation Committee

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Five subjects were selected at random from the 8 men, and a Dreiling-type double lumen tube was inserted into Treitz's ligament during fasting in the early morning. In the control group, physiological saline was subcutaneously (s.c.) administered 30 minutes before the test, then PZ and secretin (Boots Ltd., England) at 0.01 CHR U/kg/min were consecutively dripped, and the duodenal juice was collected every 10 minutes up to 120 minutes. In 5 cases of the octreotide group, 100 µg of octreotide was s.c. administered 30 minutes before the drip administration of PZ and secretin and testing was performed.

The duodenal juice was assessed for the concentrations of bile acid (3α-HSD, Enzybile 2, Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan), bicarbonate (Natelson method) (14), and lipase (BALB, DTNB method [lipase kit S., Dainihon Pharmaceutical Co., Ltd., Osaka, Japan]). The bile acid concentration was expressed as a unit of mM, while bicarbonate and lipase were expressed (mEq and IU respectively) by the excretion at each time, multiplying by the fluid volume for 10 minutes.

Also, 5 of the 8 subjects took 2,200 kcal (60 g of fat) and their feces was collected consecutively for 3 days before the start of the test. Following this, 100 µg of octreotide was s.c. administered 30 min before each meal consecutively for 7 days, and the feces was collected for the last 3 days. The obtained feces was diluted with water, homogenized, and freeze-dried. To the freeze-dried feces, 23-nordeoxy-cholic acid was added as an internal standard, then hydrolysis was conducted in an autoclave (120°C) for 3 hours, and after methylation and purification in an alumina column, the bile acids in the feces were analyzed as an acetyl derivative in a 1% XE-60 column by gas-liquid chromatography (GLC) (15). Meanwhile, as for the fatty acids in the feces, heneicosanoic acid was added to the new fresh stool as an internal standard, after reflux-extraction with chloroform-methanol under N₂ stream. Hydrolysis and methylation followed, and analysis was conducted in a 10%

EGSP column by GLC (15). The obtained amount of fatty acid was expressed as neutral fat.

Statistical analysis was made by the Mann-Whitney U-test or the paired *t* test.

Results

Changes in duodenal juice (Table 1)

1) Concentration of bile acid

At a period of 15 min before administration of PZ-secretin, no significant difference was observed in the concentration of bile acid between the control and octreotide groups. However, the bile acid concentration in the duodenal juice significantly ($p<0.05 - p<0.01$) decreased from 10 minutes to 80 minutes in the octreotide group compared with the control group. The bile acid concentration in the octreotide group decreased to zero over a period of 50 minutes to 80 minutes in some cases. Also, the bile acid concentration fell to less than 4 mM, the critical micellar concentration (16), during the 50 minutes period from 50 minutes to 100 minutes. The minimal value of duodenal bile acid concentration was recorded at 70 minutes (100 minutes after octreotide administration). The overall sum of the bile acid concentration decreased to 53.5 mM in the octreotide group, about one-quarter of the 191.0 mM decrease in the control group.

2) Bicarbonate output

At a period of 15 minutes before PZ-secretin administration, no significant difference was observed in the bicarbonate output between the control and octreotide groups. However, the bicarbonate output significantly ($p<0.05 - p<0.01$) decreased in the octreotide group during the period of 10 minutes to 120 minutes (except for the 100 minutes), as compared with the control group. The overall sum of the bicarbonate output decreased to 11.3 mEq in the octreotide group, about one-quarter of the 39.9 mEq decrease in the control group.

Table 1. Effects of Somatostatin Analogue on Duodenal Bile Acid Concentration, Bicarbonate Output, and Lipase Output

		-15	10	20	30	40	50	60	70	80	90	100	110	120	Sum
Bile acid concentration (mM)	[S]	1.32 ±1.72	7.62 * ±5.32	13.14 * ±7.3	7.5 * ±5.53	6.26 * ±3.22	1.62 ** ±1.24	0.04 ** ±0.09	0.02 ** ±0.04	0.48 ** ±0.85	3.68 ±2.78	2.26 ±0.92	4.14 * ±2.84	6.7 ±2.57	53.46 ** ±25.35
	[C]	0.76 ±0.93	26.8 ±21.3	26.7 ±12.3	20.3 ±11.4	14.7 ±5.2	11.3 ±10.3	13.2 ±12.7	8.82 ±7.9	13.8 ±12.3	10.2 ±14.6	10.2 ±9.5	18.5 ±18.1	16.5 ±16.9	191.4 ±61.57
Bicarbonate output (mEq)	[S]	0.5 ±0.3	0.28 ** ±0.36	0.23 ** ±0.12	0.84 ** ±0.54	0.75 ** ±0.33	0.77 ** ±0.29	0.96 ** ±0.78	0.8 ** ±0.78	1.28 * ±1.07	1.22 ** ±0.43	1.58 ±1.10	1.18 * ±0.40	1.42 ** ±0.27	11.32 ** ±4.47
	[C]	0.61 ±0.44	1.02 ±0.19	2.78 ±0.42	3.02 ±0.62	3.03 ±0.20	3.74 ±0.25	3.98 ±0.25	3.67 ±0.22	4.05 ±0.16	3.21 ±0.50	3.24 ±0.31	4.04 ±0.15	4.06 ±0.16	39.90 ±1.50
Lipase output (IU)	[S]	548 ±409.0	109.8 ** ±112.3	130.4 ** ±92.5	218.8 ** ±160.6	261.4 ** ±130.0	189.6 ** ±114.7	281.8 ** ±176.7	219.6 ** ±201.8	320.2 ** ±261.8	256.6 ** ±104.8	224 ** ±212.5	164.2 ** ±169.8	355.8 ** ±199.7	2,732.2 ** ±1,326.81
	[C]	508 ±250.3	716.8 ±211.4	991.8 ±200.1	886 ±189.8	722.2 ±74.9	1,041.6 ±171.3	1,045.6 ±188.4	928.4 ±170.5	723.8 ±171.0	650.2 ±124.8	496.2 ±81.2	548 ±141.0	829.2 ±109.7	9,573.8 ±1,270.66

All values were expressed as mean±SD. [S]: somatostatin-analogue administration group (n=5), [C]: control group (n=5), * $p<0.01$, ** $p<0.05$ vs. control.

Table 2. Effects of Somatostatin Analogue on Fecal Fat and Fecal Bile Acid Excretion as Measured before and after Each Meal for 7 Days

Case	Fecal fat (g/day)		Fecal bile acid (mg/day)	
	Before	After	Before	After
1	0.8	4.3	233.2	55.2
2	1.0	27.9 [†]	165.1	47.0
3	1.5	5.6	256.0	60.0
4	2.8	2.9	300.3	70.3
5	1.9	13.1 [†]	212.4	40.3
Mean	1.6	10.8	233.4	54.6*
±SD	±0.8	±10.4	±50.2	±11.6

[†]Steatorrhea was observed. *Significant ($p < 0.01$) change as compared with the value before somatostatin administration.

Maximal inhibition of bicarbonate output was recorded at 20 minutes (that is, 50 minutes after the administration of octreotide).

3) Lipase output

At all intervals of the octreotide group, except for 15 minutes before PZ-secretin administration, the lipase output showed significant ($p < 0.05$ – $p < 0.01$) decreases in comparison with the control group. The overall sum of the lipase output in the octreotide group was 2,732.2 IU, showing a significant ($p < 0.01$) decrease compared with 9,573.8 IU in the control group. The decrease in the octreotide group was about 1/3 of the control group.

Maximal inhibition of lipase output was recorded at 10 minutes (40 minutes after the octreotide administration).

Excretions of fat and bile acid in feces

As shown in Table 2, the fat excretion in the feces before administration of octreotide was 1.6 g/day and it increased to 10.8 g/day after administration. Obvious greasy stool (steatorrhea) was observed in 2 cases (case 3 and 4). On the other hand, the bile acid excretion in the feces was 233.4 mg/day before octreotide administration and it decreased to 54.6 mg/day, i.e., about 1/4 of the prior level, after octreotide administration. This was a significant ($p < 0.01$) decrease.

Discussion

When a long-acting somatostatin analogue at a dose of 50 μ g is s.c. injected, its blood concentration peaks at 30 minutes, and it shows a biological half-life of 90 minutes (17).

In the present study, the times of reaching the nadir, after the administration of octreotide were different between bicarbonate and lipase output. That is, the lowest values in acinar cell and ductal cell responses to PZ-secretin were recorded at 40 minutes and 50 minutes after analogue administration, respectively, while the minimal bile acid concentration in the duodenum was noted at 100 minutes.

Therefore, it is conceivable that the pancreatic acinar cell

and ductal cell are more sensitive to octreotide than the smooth muscles of the gallbladder. The gallbladder contraction was slower than pancreatic exocrine inhibition.

Pancreatic maldigestion and malabsorption develop when the pancreatic lipase secretion decreases to less than 10% of the normal amount (18). It is clear that pancreatic enzyme supplement by itself offers no improvement in cases of steatorrhea. Decreases in pancreatic lipase output of 1/3 to 1/4 observed in this study do not differ from those previously reported (10). Steatorrhea in cases where the analogue was administered cannot be explained solely by a decrease in the lipase excretion. Bile acid is essential for the digestion and absorption of fat. Specifically, bile acid forms a micella together with monoglycerides and fatty acids in the upper small intestine (19). The minimum concentration of bile acid needed for micelle formation is defined as the critical micellar concentration (abbreviated as CMC) (16). Primary biliary cirrhosis, cholestatic jaundice, liver cirrhosis, etc. which cause deficiency of biliary secretion, have been pointed out as diseases which lower the bile acid concentration in the micellar phase of the small intestine (20–24). It is estimated that the bile acid concentration in the small intestine has become lower than the CMC (16). In the present study, the bile acid concentration in the duodenal juice due to exogenous PZ-secretin stimulation became 0 mM at a certain time after analogue administration, and it remained less than the CMC for 60 minutes. Moreover, it is noted that pancreatic bicarbonate secretion, which is an important factor in maintaining the upper intestinal pH during fat digestion and absorption, is reduced to about 1/4 that of the control group after administration of octreotide. In fact, it has been reported (25) that bicarbonate output from pancreatic fistulas is reduced by 45% after the administration of octreotide acetate. The duodenal pH determinant consists mainly of gastric acid output and bicarbonate secretion from pancreas. Therefore, the reduced bicarbonate output is supposed to lower the intestinal pH. Therefore, we may consider the possibility that a decrease in the lipase output, in addition to the decreases in bicarbonate excretion and bile acid concentration, may act contributively or synergistically, resulting in the development of fat maldigestion and malabsorption. Moreover, it has been suggested (3) that the fat absorption in the small intestine may be inhibited by the analogue, although we have not examined this possibility.

One case (case 4) showed no steatorrhea during octreotide administration. Fat digestion must have been completed before the octreotide inhibited the pancreatic and biliary functions in case of the facilitated gastric emptying. The details remain unclear, however, as we were unable to investigate the gastric emptying.

In the present study, 100 μ g of the analogue was s.c. injected before each meal, and consequently steatorrhea was observed. Accordingly, a method for administering less than 100 μ g may be worth considering in order to reduce steatorrhea. Also, as pointed out by Creutzfeldt et al (10), steatorrhea due to the analogue administration may not persist for a long time. It seems that due attention should be paid to minor adverse reactions such as steatorrhea in the beginning of analogue

administration.

From the above results, we conclude that octreotide administration to healthy subjects decreases bicarbonate, lipase secretion and reduces the duodenal bile acid concentration. Consequently, it is conceivable that the synergic inhibition of biliary and pancreatic functions may cause steatorrhea during octreotide administration in humans.

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