Postprandial gall bladder motility and hormone release during intermittent and continuous subcutaneous octreotide treatment in acromegaly

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Abstract

Repeated daily injections of the somatostatin analogue, octreotide (SMS201-995, Sandostatin) are an effective treatment for acromegaly, but lead to gall stone formation in about 50% of cases during longterm treatment. This is probably because of impaired gall bladder contraction. This study examined whether the timing of intermittent injections in relation to meals, or alternatively, continuous 24 hour subcutaneous octreotide infusion (CSOI) might avert adverse effects on gall bladder contraction. In six patients with active acromegaly, gall bladder volume, plasma cholecystokinin (CCK), and pancreatic polypeptide (PP) were measured in the fasting state and after consumption of a fatty meal. Measurements were made on five separate days: (a) without treatment, (b) 45 minutes after 100 µg octreotide given subcutaneously, (c) four hours after 100 µg octreotide given subcutaneously, (d) eight hours after 100 µg octreotide given subcutaneously, and (e) during CSOI of 300 µg/24 h for two weeks. Without treatment, postprandial gall bladder contraction was 86.2 (2.1%). Fasting gall bladder volume increased after octreotide injection and was almost doubled during CSOI. Octreotide injections impaired postprandial gall bladder contraction as well as CCK and PP release for at least four hours. Eight hours after injection and during CSOI, postprandial gall bladder contraction was partly restored (43.4% and 50.8% respectively). Postprandial CCK release was normal at eight hours after injection but very low during CSOI. PP release was suppressed by each mode of octreotide treatment. This study indicates that octreotide injections impair postprandial gall bladder contraction for at least four hours. Eight hours after injection and during CSOI, gall bladder contraction is partly restored.

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Intermittent subcutaneous treatment with a longacting somatostatin analogue, octreotide (SMS201-995, Sandostatin) is an effective treatment for patients with acromegaly.¹⁻³ Octreotide is usually given by intermittent subcutaneous injection of 100-500 µg twice daily or three times daily. Continuous subcutaneous octreotide infusion (CSOI) of 300-1500 µg/24 h is probably more effective in suppressing growth hormone secretion.^{4,5} An important side effect of longterm octreotide treatment with intermittent injections

is a high incidence, up to 50%, of gall stone formation during one year of treatment.⁶⁻⁹ The rate of gall stone formation during CSOI has yet to be discovered, but is probably lower.⁴ A high occurrence of gall stones is also found in patients with somatostatinoma, the natural equivalent of longterm somatostatin treatment.¹⁰ Like natural somatostatin, octreotide inhibits postprandial gall bladder contraction, release of cholecystokinin (CCK), and pancreatic polypeptide (PP) when given just before a meal.¹¹⁻¹³ Impaired postprandial gall bladder contraction is a risk factor for gall stone formation.¹⁴⁻¹⁶

We examined the effect of varying the intervals between octreotide injection and meal ingestion on fasting and postprandial gall bladder motility and on plasma CCK and PP concentrations in patients with acromegaly. These findings were used to see whether appropriate timing of octreotide injections with respect to meal ingestion might avert impaired gall bladder contraction. In addition, we examined the effect of CSOI on fasting and postprandial gall bladder motility and hormone release in these patients.

Patients and methods

SUBJECTS

Six patients with active acromegaly, requiring octreotide treatment, were enrolled in the study. All patients had typical clinical features of the acromegaly syndrome, high circulating growth hormone concentrations, which were not suppressed below 2 µg/l after an oral glucose load, and insulin like growth factor-1 (IGF-1) or somatomedin-C plasma concentrations above the mean 2 (SD) for age. Table I shows patient characteristics. Ultrasound examination of the gall bladder, bile ducts, and liver was performed before the study and showed no stones, sludge, or other abnormalities. None of the patients had had abdominal surgery previously. None of the patients were pregnant at the time of the study or had taken any drug which could potentially interfere with gall bladder motility. Body weight was stable during the three months preceding the study. All patients gave written informed consent. The study protocol was approved by the ethical committee of our hospital.

PROTOCOL

Postprandial gall bladder contraction as well as plasma CCK and PP concentrations were assessed on five separate days with at least one day in between to allow for degradation of

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TABLE 1 Characteristics of six patients with acromegaly. Insulin like growth factor-1 (IGF-1) concentrations were verified before inclusion in the study

Patient	Sex	Age (y)	Body weight (kg)	IGF-1 (ng/ml)	Previous treatment (length of treatment) (month)
A	F	31	89	708	None
B	M	45	108	1031	PMS irradiation bromocriptine (108)
C	F	52	83	583	PMS irradiation octreotide thrice daily (6)
D	M	61	83	340	Octreotide thrice daily (31)
E	F	55	78	294	PMS irradiation octreotide thrice daily (10)
F	M	28	97	570	Octreotide four times daily (28)

Patients C to F were treated with subcutaneous octreotide injections of 100 µg until two weeks before the study started. PMS=pituitary micro surgery.

octreotide ($T_{1/2}$ =80–100 minutes).¹⁷ The first measurement was made after two weeks without any treatment. The second, third, and fourth measurement (on separate days) started at 45 minutes, four hours, and eight hours respectively after a single subcutaneous injection of 100 µg octreotide (Sandostatine, Sandoz AG, Basle, Switzerland). The fifth measurement was made after two weeks of continuous subcutaneous treatment with 300 µg octreotide/24 h with an ambulatory pump (CADD-1 Ambulatory Infusion Pump, Pharmacia Deltec Inc, St Paul, USA). This measurement was taken while the pump was giving octreotide.

Measurements

After an overnight fast, gall bladder volume was measured by real time ultrasonography (SDR 1500, Philips Ultrasound Inc, California, USA: 5.0 MHz transducer). Sagittal and transverse scans of the gall bladder at its largest dimensions were obtained. Subsequently, after consumption of a test meal, gall bladder images were made every 15 minutes for 2 hours. These images were stored on video tape and processed by a MS-DOS computer, using a video grabber, and processing software (IBAS, Kontron GmbH, Munich, Germany). Gall bladder volume was calculated with the sum of cylinders method.^{18,19} The test meal consisted of 1 slice of white bread, 5 g margarine, 50 g cheese, 1 boiled egg, 200 ml yoghurt, and 50 g glucose. This is equivalent to 30 g fat, 30 g protein, and 70 g carbohydrate and gives a physiologic stimulation of gall bladder contraction and cholecystokinin release. Fasting volume (mean of measurements at 15 and 0 minutes before test meal; V_0 in ml) and resi-

dual postprandial volume were measured as characteristic of gall bladder motility. Residual gall bladder volume (V_{res} in ml) was defined as the resulting volume after maximum response to a test meal. In gall bladder filling after a test meal, V_{res} reflects maximum gall bladder volume. As indices of postprandial gall bladder contraction, maximum decrement of gall bladder volume in ml and percentage (ΔV_{max} ml and ΔV_{max} %) and integrated gall bladder contraction (expressed as ml.120 min) were calculated.

Blood samples were taken in the fasting state, at -15 and 0 minutes and, after consumption of the test meal, every 15 minutes for 2 hours. Blood was collected in ice chilled tubes. Plasma was stored at -20°C until analysis. CCK and PP plasma concentrations were measured by sensitive and specific radioimmunoassays, as described previously.^{20,21} Indices of CCK and PP release were basal concentration (mean of concentrations at -15 and 0 minutes), maximum increase (Δ CCK and Δ PP), and integrated CCK and PP release (expressed as pmol.l⁻¹.120 min). Plasma octreotide concentrations (pg/ml) were assessed by radioimmunoassay (Sandoz, Basle, Switzerland), immediately before consumption of the test meal (at 0 minutes) for measurements at 45 minutes, 4 hours, and 8 hours after subcutaneous octreotide injection. Plasma octreotide concentrations during CSOI were measured in the fasting state and, after consumption of the test meal, every 30 minutes for two hours.

Statistical analysis

Results are shown as mean (SEM). Differences between the effects of the five experimental conditions on gall bladder volume, hormone release, and octreotide values were assessed by two way repeated measures of analysis of variance. When a statistically significant difference was detected, results were further analysed by Fishers's LSD test. Statistical significance was defined as a two tailed probability of less than 0.05.²²

Results

GALL BLADDER CONTRACTION

Table II shows indices of gall bladder contraction and Figure 1 shows gall bladder contraction curves. Without treatment, postprandial gall bladder contraction was 86.2 (2.1)% or 36.2 (5.7)

TABLE II Indices of gall bladder contraction, measured on five separate days: without medication, at 45 minutes, 4 hours, and 8 hours after subcutaneous injection (SC) of 100 µg octreotide and after two weeks of continuous subcutaneous octreotide injection (CSOI) of 300 µg/24 h

Indices	No medication	45 minutes after 100 µg SC injection	4 hours after 100 µg SC injection	8 hours after 100 µg SC injection	Continuous SC infusion 300 µg/24 h
V_0 (ml)	42.1 (6.3)†‡	52.3 (10.0)§	57.2 (10.6)*§	50.0 (7.9)§	81.5 (9.2)*†‡§
V_{res} (ml)	5.6 (1.3)†‡	57.5 (10.0)*§	58.7 (14.0)*§	26.9 (6.7)†‡	41.8 (10.6)*
ΔV_{max} (ml)	36.2 (5.7)†‡	-5.1 (5.0)*§	-1.5 (8.6)*§	23.0 (7.4)†‡	39.7 (6.3)†‡
ΔV_{max} (%)	86.2 (2.1)†‡	-14.8 (12.5)*§	1.2 (14.6)*§	43.4 (10.4)*†‡	50.8 (8.5)†‡
AUC contraction (ml.120 min)	-3134 (408.3)†‡	236.2 (233.5)*§	-32.3 (622.6)*§	-1711 (651.8)†	-2821 (917.6)†‡

Significant difference compared with: *before treatment, †45 minutes after injection, ‡4 hours after injection, §8 hours after injection, ||two weeks continuous subcutaneous octreotide infusion.

V_0 =fasting volume, V_{res} =residual volume, ΔV_{max} =maximal decrement of gall bladder volume, AUC contraction=integrated gall bladder contraction.

Figure 1: Gall bladder volume before and after a test meal during five experimental conditions. ● = before treatment, ○ = 45 minutes after injection of 100 µg octreotide, ▲ = 4 hours after injection, + = 8 hours after injection, △ = during continuous subcutaneous octreotide infusion of 300 µg/24 h for two weeks.

ml. Forty five minutes and four hours after subcutaneous octreotide injection (measured on separate days), postprandial gall bladder contraction was stopped. Eight hours after octreotide injection, postprandial gall bladder contraction was partially restored. Fasting gall bladder volume increased after injections, compared with the volume before treatment. After two weeks of CSOI of 300 µg/24 h, fasting gall bladder volume had increased almost twofold to 81.5 (9.2) ml whereas postprandial gall bladder contraction was 50.8 (8.5)% or 39.7 (6.3) ml. Eight hours after injection of octreotide and after two weeks of CSOI, ▲V_{max} ml (as index for the amount of bile expelled to the duodenum during a meal) was not significantly different compared with that of gall bladder contraction without treatment (Fig 2).

CHOLECYSTOKININ AND PP RELEASE

Table III shows indices of plasma CCK and PP release. Basal CCK concentrations did not change during octreotide treatment. Postprandial CCK release was suppressed for at least four hours after injection (Fig 3). Eight hours after injection, integrated postprandial CCK release was not significantly different compared with the first measurement, without treatment (Fig 4). During CSOI, postprandial CCK release was suppressed. Integrated CCK release was only 46.0 (22.5) pmol CCK.l⁻¹.120 min compared with 256.8 (30.1) pmol CCK.l⁻¹.120 min without treatment. Basal PP concentrations and postprandial PP release were suppressed by

Figure 2: Maximum decrement of gall bladder volume (ml) after a test meal, during five different experimental conditions. 45 minutes, 4 hours, and 8 hours refer to the time when the meal was given after subcutaneous injection of 100 µg octreotide. CSOI = gall bladder contraction during continuous subcutaneous octreotide infusion.

intermittent injections as well as by CSOI (Fig 5).

PLASMA OCTREOTIDE CONCENTRATION

Table III shows plasma octreotide concentrations. As expected, plasma octreotide concentrations were lowest eight hours after injection. During CSOI, octreotide concentrations were comparable with values at four hours after injection. Octreotide concentrations during CSOI did not change for two hours after meal consumption (results not shown).

Discussion

This study showed that fasting gall bladder volume increased after treatment with octreotide. Fasting gall bladder volume had virtually doubled from 42.1 ml in octreotide free conditions to 81.5 ml after two weeks of CSOI. Increased fasting gall bladder volume during octreotide might be a result of decreased gall bladder muscle tone or because of the absence of interdigestive gall bladder contraction, which takes place in the fasting state, in close association with the intestinal migrating motor complex.²³ Decreased sphincter of oddi function might also account for increased fasting volume.²⁴ In comparison with a control group of 20 normal subjects, studied in our laboratory, patients with acromegaly had large fasting volumes, even without treatment (18.9 (1.6) ml) v 42.1 (6.3 ml); p<0.002.²⁵ Similarly, increased fasting gall bladder volumes have been reported in obese, tall, and muscular subjects.²⁶ Therefore, increased fasting volumes in patients with

TABLE III Basal cholecystokinin (CCK) and pancreatic polypeptide (PP) concentrations (pmol/l), maximum increase, integrated release (pmol/l × 120 min), and plasma octreotide concentrations (pg/ml) before treatment, at 45 minutes, 4 hours, and 8 hours after subcutaneous injection of 100 µg octreotide and after two weeks of CSOI of 300 µg/24 h

Indices	No medication	45 minutes after 100 µg SC injection	4 hours after 100 µg SC injection	8 hours after 100 µg SC injection	Continuous SC infusion 300 µg/24 h
Basal CCK	2.0 (0.3)	1.6 (0.3)	1.8 (0.4)	1.9 (0.3)	1.8 (0.2)
Maximum increase CCK	2.6 (0.2)*†‡§	0.4 (0.2)*§	1.0 (0.2)*§	2.0 (0.2)*†‡	0.7 (0.1)*†‡§
AUC CCK	256.8 (30.1)*†‡§	-15.5 (16.2)*†‡§	76.0 (20.8)*†‡§	192.8 (30.0)*†‡	46.0 (22.5)*§
Basal PP	26.1 (3.2)*†‡§	13.6 (1.9)*	9.6 (1.5)*	9.1 (1.6)*	7.8 (1.2)*†
Maximum increase PP	98.3 (13.9)*†‡§	0.2 (0.1)*	2.4 (0.8)*	4.6 (1.6)*	9.6 (5.8)*
AUC PP	8738.8 (1458.6)*†‡§	-367.5 (69.0)*	-47.5 (50.6)*	217.5 (109.3)*	655.0 (431.9)*
Octreotide	-	2089.5 (264.6)*§	857.2 (67.1)†	320.0 (77.2)†	1025.2 (270.8)†§

Significant difference compared with: *before treatment, †45 minutes after injection, ‡4 hours after injection, §8 hours after injection. ||two weeks continuous subcutaneous octreotide infusion. AUC CCK and AUC PP = integrated hormone concentrations.

Figure 3: Plasma cholecystokinin concentrations (pmol/l) before and after ingestion of a test meal. For symbols see Fig 1.

acromegaly might be explained by their large body size.

We found that patients with acromegaly not receiving treatment, were able to contract their gall bladder almost completely after a meal. This is in agreement with other studies.^{12,27} It would seem that acromegaly as such does not directly impair gall bladder contraction. Our study also showed that postprandial gall bladder contraction was suppressed for at least four hours after octreotide injection. Delayed gastric emptying is not responsible for this finding since octreotide, in contrast with somatostatin, slightly accelerates gastric emptying of a mixed meal.²⁸ Like others, we saw postprandial gall bladder filling rather than contraction at 45 minutes and four hours after injection.¹² At eight hours after injection, postprandial gall bladder contraction (ml) was not significantly different compared with contraction without treatment or with contraction after two weeks of CSOI. This could be because of the small number of patients studied, but it is in agreement with the results of Hopman *et al*, who measured postprandial gall bladder contraction in patients on longterm (six months) intermittent injection treatment. At eight hours after the last injection they found 17.0 ml emptying, which was not significantly different from postprandial gall bladder contraction without treatment.²⁷

Low plasma octreotide concentration and increased fasting volume may explain improved gall bladder contraction. Gall bladder contraction during longterm treatment was still greatly

Figure 4: Integrated CCK release (pmol/l × 120 min) during five different experimental conditions. 45 minutes, 4 hours, and 8 hours refer to the time when the meal was given after subcutaneous injection of 100 µg octreotide. CSOI = gall bladder contraction during continuous subcutaneous octreotide infusion. CCK release during continuous infusion is remarkably low.

Figure 5: Plasma pancreatic polypeptide concentrations (pmol/l) before and after ingestion of a test meal during five different experimental conditions. For symbols see Fig 1. PP release is suppressed by each octreotide administration mode and even below basal values.

suppressed (19%) at 45 minutes after injection.²⁷ This study suggests that CSOI (50–8% contraction) or adequate timing of injections with respect to meals might, at least partially, preserve gall bladder contraction and thereby might reduce the risk of gall stone formation.

After each mode of octreotide treatment, postprandial residual gall bladder volume increased. In pregnancy²⁹ and obesity,³⁰ increased fasting and postprandial residual gall bladder volumes are associated with increased risk of gall stone formation. In tall and muscular subjects, fasting and residual gall bladder volumes are also increased but, as far as known, without increased risk of gall stone formation.²⁶ Therefore, the role of increased fasting and residual gall bladder volume – as described in this study of patients with acromegaly receiving octreotide treatment – in the formation of gall stones remains uncertain.

The effect of octreotide on gall bladder motility may not be crucial in the formation of gall stones. Somatostatin and octreotide also have an effect on bile composition. In experiments with animals, bile salt independent canalicular flow is reduced and biliary lipid concentration is enhanced.^{31–35} This increases biliary cholesterol content and favours nucleation of cholesterol monohydrate crystals.⁹ Potential differences in this respect between intermittent octreotide injection and CSOI have yet to be studied.

Gall bladder contraction is regulated by an interaction of the myenteric plexus with intestinal hormones. CCK is important for mediating postprandial gall bladder contraction and acts in physiological doses by the cholinergic neurons of the plexus, as shown in guinea pigs.³⁶ In the same species, in vitro, somatostatin does not inhibit gall bladder contraction induced by CCK octapeptide or acetylcholine³⁷ but it inhibits electrically induced gall bladder contraction, probably by a reduction of acetylcholine release.³⁸ The same finding was made in dogs.³⁹ This indicates that somatostatin – and probably also octreotide – has no direct effect on the gall bladder but exerts its inhibitory action by the myenteric plexus. Moreover, octreotide inhibits the release of CCK from the duodenum.

PP is produced in the pancreas and its release is under cholinergic control and can be evoked

by a meal. PP inhibits gall bladder contraction by an inhibiting action on cholinergic pathways.⁴⁰ Postprandial PP release was at a maximum in the untreated state. After each injection of octreotide, fasting PP concentrations and postprandial PP release were suppressed, even below basal values. Therefore, it is concluded that increased fasting gall bladder volumes and inhibition of postprandial gall bladder contraction during octreotide treatment are not mediated by PP. Plasma octreotide and PP concentrations confirmed patient compliance to the study protocol.

Acromegaly patients generally use three octreotide injections daily, usually given before breakfast in the morning (8:00), afternoon (16:00), and late in the evening (24:00). This study suggests that if the early morning injection is taken after breakfast, the gall bladder can empty partially (43.4%). Gall bladder contraction during lunch and dinner (within 4 to 6 hours of the early morning and afternoon injection), however, remains suppressed. Good gall bladder contraction after breakfast is important because gall bladder bile has the highest cholesterol saturation index and concentration at that time and cholesterol crystals might precipitate easily.⁴¹ In the subgroup of patients who are treated with two injections daily, adequate gall bladder contraction might also be achieved after dinner. At eight hours after injection, about 70% of maximum gall bladder contraction was achieved at 45 minutes after the test meal. This might suggest that octreotide injections should be given at least 45 minutes after a meal. During CSOI, postprandial gall bladder contraction is partially preserved during all meals.

In conclusion, this study shows that postprandial gall bladder contraction and CCK and PP release are greatly impaired for at least four hours after injection of octreotide. Eight hours after octreotide injection, gall bladder contraction is partially restored and CCK release is completely restored. Also during CSOI, postprandial gall bladder contraction is partially restored while CCK release remains low. Prospective studies should show whether appropriate timing of octreotide injections with respect to meal ingestion, or alternative treatment schedules, like CSOI, might lessen the risk of gall stone formation during long term octreotide treatment.

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