Effect of the somatostatin analog octreotide on gastric mucosal function and histology during 3 months of preoperative treatment in patients with acromegaly

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Abstract

Objective: To study the effects of the somatostatin analog octreotide on gastric mucosal function and histology during short-term (3 months) preoperative treatment in patients with acromegaly.

Methods: 10 patients were studied before treatment with octreotide (pre-tx), on day 1 of 300 μg octreotide/day (d300), after 1 week on 300 (w300), 600 (w600) or 1500 (w1500) μg octreotide/day, and after an additional 2.5 months on 1500 μg octreotide/day (M3). An 8 h gastrin profile was obtained and ambulatory intragastric 23 h pH-metry carried out at the indicated time points. Gastroscopy was performed at pre-tx and M3 and multiple mucosal biopsy specimens taken.

Results: The mean serum gastrin concentration at first declined during octreotide therapy to a nadir at w1500, then recovered despite ongoing therapy (probably in response to reduced gastric acidity) and was similar to pre-tx values at M3 (mean ± S.E.: 87 ± 26, 50 ± 11 and 98 ± 46 ng/l for pre-tx, w1500 and M3 respectively; P < 0.05, pre-tx vs w1500). Gastric acidity had also declined at d300 (P < 0.05, d300 vs pre-tx), then recovered (despite the increase in the octreotide dose), but declined again at M3 (mean pH (95% confidence interval): 2.4 (1.7–3.2), 3.3 (2.4–4.3), 2.6 (1.8–3.5, n=8) and 2.9 (1.6–4.2, n=7) at pre-tx, d300, w1500 and M3 respectively). The gastrin concentration at M3, although similar to pre-tx values, remained inadequately low for the reduced gastric acidity. The reduction in gastric acidity was marked during the daytime (0900–2200 h; P < 0.01, d300 vs pre-tx and P = 0.028, M3 vs pre-tx). However, while the stimulated postprandial gastric acid secretion was reduced at d300 (P < 0.01, d300 vs pre-tx) and at M3 (n=7; P=0.027, M3 vs pre-tx), fasting and preprandial acidity was not affected. During the night, gastric acidity was reduced from 2200 to 0300 h, but the reduction was less marked than during the daytime. Paradoxically, the physiological intermittent late nocturnal reduction in acidity (‘pH peaks’ (0300–0800 h)) was abolished rather than enhanced. No patient acquired new Helicobacter pylori infection. The mean gastritis scores for antrum and body (n=8, Sidney classification) increased marginally from 1.7 to 1.9 (chronicity) and from 0.7 to 0.9 (atrophy), while the activity score was slightly reduced from 1.2 to 1.0.

Conclusions: Three months of preoperative octreotide treatment profoundly and persistently altered gastric mucosal function (gastrin suppression, reduced acidity), but caused only minor variations in the pre-existing gastritis scores.

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Introduction

The somatostatin analog octreotide is used for long-term treatment of acromegalic patients in whom previous therapy has failed to normalize serum growth hormone (GH) concentration (1, 2). More recently, it has also been used for preoperative suppression of GH secretion and reduction of tumor size (2–4). Octreotide also suppresses gastrin (5, 6) and gastric acid secretion (7), potentially promoting colonization of the gastric mucosa with Helicobacter pylori (8) and the development of chronic active and ultimately atrophic gastritis (9). Both atrophic gastritis and H. pylori infection are potentially precancerous conditions (10–13). However, the significance of octreotide-induced changes and their consequences during long-term treatment are not entirely clear (14–18), and their development during short-term (e.g. preoperative) treatment has not been studied. Moreover, rapid restoration of gastric acid secretion despite ongoing treatment has been reported in one short-term study (17). In contrast, we have observed that gastric acid secretion was still suppressed after 3.5 years of continuous treatment (18).
The development of chronic atrophic gastritis could be of particular importance in acromegalic patients, as acromegaly is associated with an increased incidence of gastrointestinal malignancies, including gastric adenocarcinoma (19, 20). Hence, it is necessary to define more precisely the gastrointestinal risk profile of short- and long-term somatostatin analog therapy in these patients. We therefore investigated prospectively the effect of octreotide on gastrin secretion, 23 h intragastric pH, and gastric mucosal histology in 10 acromegalic patients during 3 months of preoperative octreotide therapy.

Subjects and methods

Study design

Ten acromegalic patients (Table 1) were treated with octreotide before surgery. Acromegaly was diagnosed according to clinical criteria, non-suppressibility of plasma GH concentration to below 1 μg/l during an oral glucose load (100 g), and elevated plasma insulin-like growth factor-1 (IGF-I) concentration (mean of three samples at 0800, 0900 and 1000 h). Parietal cell antibodies were negative before therapy in all but one patient (patient 3). Octreotide therapy began with 3·100 μg/day s.c. at 0800, 1600 and 2400 h. The dose was increased to 3·200 μg/day and 3·500 μg/day in weekly intervals and kept on 1500 μg/day for a total treatment duration of at least 3 months (6 months in six patients).

An 8 h profile (0800–1600 h, hourly samples) of serum gastrin concentration was obtained before therapy (pre-tx), on the first day on 300 μg/day (d300), after 1 week on 300 (w300), 600 (w600) and 1500 μg/day (w1500), as well as after 3 months of therapy (M3), and again 6 weeks after surgery. In the six patients on octreotide therapy for 6 months (M6), an additional 8 h gastrin profile was obtained at M6. Ambulatory 23 h intragastric pH-metry was performed concomitantly with the gastrin profiles before treatment and during octreotide therapy. No patient received any medication that interfered with gastric acid secretion, either during the 12 months before or during the study period. No signs or symptoms related to upper gastrointestinal disease were reported, either before or during octreotide therapy (except for the first 3 days, when bloating, upper abdominal discomfort and occasional loose stools occurred in some patients). Gastroscopy was performed, during which multiple biopsy specimens of the gastric mucosa were taken, and H. pylori IgG antibodies were evaluated before octreotide therapy and at M3.

Informed written consent was obtained from all patients. The study was performed according to the guidelines of the Declaration of Helsinki. The study protocol was approved by the hospital ethical committee.

Hormone and antibody determinations

Blood was centrifuged immediately after withdrawal, and the serum or plasma was stored at −20 °C until assayed in duplicate using commercially available RIAs: serum gastrin (ICN Pharmaceuticals, Orangeburg, NY, USA), serum GH (Sorin, Saluggia, Italy; IRP 80/505), acid/ethanol-extracted plasma IGF-I (Nichols Institute, San Juan Capistrano, CA, USA; IRP 87/518). The intra- and interassay coefficients of variation were 8.0 and 8.8% for gastrin, 4.4 and 3.4% for GH, and 1.6 and 11% for IGF-I. Assay sensitivity was 3.3 ng/l for gastrin, 0.5 μg/l for GH and 0.06 μg/l for IGF-I. Serum H. pylori IgG antibody titer was determined by ELISA (Serion, Würzburg, Germany). Sensitivity, specificity, positive and negative predictive value were 90.2, 97.8, 91.8 and 97.4% respectively. Parietal cell antibodies were determined by indirect immunofluorescence, using a trivalent antihuman immunoglobulin and monkey gastric mucosa (BIOS, Munich, Germany).

Table 1 Characteristics of 10 patients with acromegaly

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>H. pylori</th>
<th>Octreotide treatment (months)</th>
<th>Mean GH* (μg/l)</th>
<th>Mean IGF-I† (μg/l)</th>
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<td>10.7</td>
<td>1027</td>
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</table>

*Mean GH (μg/l) during the 8 h profile (0800–1600 h).
†IGF-I (μg/l), mean of three values (0800, 0900, 1000 h). Normal IGF-I concentrations (95% confidence interval): age 20–40 years, males 83.3–378.0, females 112.5–450.0; age > 40 years, males 54.0–328.5, females 141.8–389.3 μg/l.
‡The high IGF-I concentration in this patient was confirmed by repeated determinations.
**Gastric mucosal histology**

Gastroscopy (GIF Q20; Olympus, Hamburg, Germany) was performed by one of us (UP), and five biopsy specimens each were taken from the antrum, body and fundus. The biopsy specimens were fixed immediately after extraction in 10% buffered formalin and embedded in paraffin. Serial sections (2 µm) were stained with hematoxylin–eosin. Inflammatory alterations were graded as absent (0), mild (1), moderate (2) or marked (3). Chronic active inflammation was defined as infiltration of the lamina propria by lymphocytes and plasma cells as indicators of chronicity and neutrophilic granulocytes as indicators of activity. The detection of *H. pylori* was based on the identification of microorganisms with appropriate morphology, localization and staining characteristics (Warthin–Starry). The specimens were assessed according to the Sidney classification (21). Interobserver agreement in the histopathological assessment of *H. pylori* infection, chronicity and activity of the inflammation is high. In contrast, for the evaluation of mucosal atrophy, interobserver agreement is low (22). Histological findings were therefore independently determined by two pathologists, who were blinded for the time points of the evaluation. Any difference in interpretation was discussed until a common conclusion was found.

**Intragastric acidity**

Ambulatory 23 h intragastric pH-metry was performed as previously described and as generally recommended (23). In brief, a miniaturized combined glass pH electrode (GK2801C; Radiometer, Copenhagen, Denmark) connected to a solid-state long-term recorder (LZ105, memory capacity 128 kByte; Kaufhold, Berlin, Germany) was inserted through one nostril into the gastric corpus region under fluoroscopic control and positioned approximately 10 cm below the lower esophageal sphincter. Measurements started at 0900 h after an overnight fast. The data were sampled and stored at a rate of 30/min (43200 pH values per 24 h). Breakfast (1000 h), lunch (1200 h), snack (1500 h) and dinner (1800 h) were standardized during the recording. Alcohol and smoking were not allowed.

**Statistics**

The mean group gastrin concentration was calculated using the individual 8 h median values. For comparison of intragastric pH values before and during octreotide therapy, the individual means of hourly median pH values for the entire observation period (23 h) were calculated (24). The individual mean daytime (0900–2200 h, 13 h) and night-time (2200–0800 h, 10 h) pH values as well as the time periods of intragastric pH with values higher than 3 were also calculated (25).

Significance of difference was calculated by Wilcoxon’s signed rank test for paired samples. Adjustment for repeated comparisons was made according to Holm-Bonferroni: \(P<0.05\) was considered significant for the calculation of the first comparison and \(P<0.025\) for the subsequent comparison. pH-metry data were evaluated using a dedicated software package developed by one of us (CE), and all other calculations were performed using Statistica 5.0 software (Statsoft Inc., Tulsa, OK, USA).

**Results**

**Gastrin**

Nine of the 10 patients were normogastrinemic before therapy, as shown by a fasting gastrin concentration (mean of three samples taken at 0800 h, 0900 h and 1000 h) below 100 ng/l. In one patient, gastrin concentration was elevated, probably because of *H. pylori*-positive gastritis (see Table 5). The mean 8 h serum gastrin concentration declined significantly during octreotide therapy to a nadir at w1500 (Table 2). However, at M3 and M6 (six patients) serum gastrin had recovered to a concentration similar to pre-tx. It remained similar to pre-tx 6 weeks after surgery (see percentage values in Table 2). Patient 3 had an unexplained high gastrin concentration at M3. When these values were excluded, the mean gastrin concentration of the remaining nine patients was still similar to pre-tx at M3, M6 and after surgery (62, 90 and 83% of pre-tx respectively; all not significantly different from pre-tx). The changes were similar in patients with and without pre-existing *H. pylori* infection (individual data not shown).

Octreotide inhibited both fasting (0800–1000 h) and meal-stimulated (1000–1200 h and 1200–1400 h) gastrin secretion. The mean area under the curve for gastrin expressed as a percentage of pre-tx at w300, w600 and w1500 respectively was 63, 64 and 57% (fasting) and 69, 63 and 49% (postprandially), although only the values at w1500 were significantly different from pre-tx (fasting \(P<0.05\) and postprandial \(P<0.02\)).

**Intragastric acidity**

The mean 23 h pH values had already increased (i.e. intragastric acidity diminished) significantly on the first day of treatment (Table 3, Fig. 1). With ongoing therapy and despite the increase in the octreotide dose, the mean 23 h pH declined again and was not significantly different from pre-tx at w300, w600 and w1500. However, after 3 months of therapy, the 23 h mean pH had again increased. The changes were similar in *H. pylori*-positive and -negative patients (individual data not shown). The pH increase was more pronounced during the day than during the night (Table 3, middle panel). Before octreotide therapy, pH values above 3 were registered during 28 and 28.5% of the daytime and night-time period respectively. At M3 pH values
above 3 were recorded in 55% of the daytime period, while all-night pH values above 3 remained similar to pre-tx (29% of the time period). However, closer inspection of the data revealed that, in fact, pH values were also moderately increased during the first part of the night (Fig. 1, lower panel). In contrast, during the second part of the night, the physiological nocturnal pH increases were paradoxically abolished, and hence the late nocturnal pH was lower rather than higher than pre-tx values.

During the day the effect of octreotide on gastric acid secretion was mainly due to a reduction in meal-stimulated intragastric acidity (Table 4). This was significant at d300 and just failed to reach significance at M3 (P = 0.027, pre-tx vs M3, n = 7). Changes in fasting and preprandial acidity (before breakfast and dinner) were not significant. (Breakfast was served at 1000 h and lunch at 1200 h. Hence, there was no fasting preprandial time period before lunch).

Gastric mucosal histology

The histopathological Sidney scores for antrum and body mucosa are given in Table 5. Before therapy, gastritis (moderate to marked inflammatory infiltrates) was present in the four patients with H. pylori infection. None or only mild infiltration was seen in the other patients (except patient 8, who had moderate lymphoplasmacellular infiltration). Comparison of histopathological results of patients with gastroscopic evaluation before octreotide therapy and after 3 months of therapy (n=8) showed only minor variations in the activity score. The mean score for chronicity and atrophy in the antral mucosa, and for activity and atrophy in the body mucosa increased slightly after 3 months. Four of the six

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<th>w300</th>
<th>w600</th>
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<th>M3</th>
<th>M6</th>
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<td>198</td>
<td>243</td>
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</table>

Mean pH of pre-tx

87 ± 26 65 ± 9 63 ± 16 63 ± 21 50 ± 11* 98 ± 46 69 ± 22 72 ± 25

Percentage of pre-tx

– 85 73 72 57 113 106 113

Table 2 Gastrin concentration (ng/l, 8 h median and group mean ± s.e.) before and during octreotide therapy as well as after surgery (post-op)

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<th>Patient</th>
<th>Pre-tx</th>
<th>d300</th>
<th>w300</th>
<th>w600</th>
<th>w1500</th>
<th>M3</th>
<th>M6</th>
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</table>

Mean pH of pre-tx

87 ± 26 65 ± 9 63 ± 16 63 ± 21 50 ± 11* 98 ± 46 69 ± 22 72 ± 25

Percentage of pre-tx

– 85 73 72 57 113 106 113

1 Determination failed for technical reasons.
2 Patients 1, 4, 5 and 6 were treated for 3 months only.
3 Patient 1 refused surgery, patient 5 was lost to post-operative follow-up.
4 Percentage of pre-tx is pairwise calculated for n = 8, n = 6 and n = 8 for d300, M6 and post-op respectively.
5 P < 0.05, w1500 vs pre-tx.

Table 3 Means of hourly pH medians, before and during octreotide therapy. Data are given for the 23 h period, as well as for daytime (0900–2200 h) and night-time (2200–0800 h). The values in parentheses are 95% confidence intervals.

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<th>pH</th>
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<td>Post-op</td>
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<tr>
<td>Daytime</td>
<td>2.5 (1.6–3.4)</td>
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<tr>
<td>Night-time</td>
<td>2.6 (1.8–4.3)</td>
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</table>

1 Percentage change vs pre-tx was calculated for n = 8 (w1500) and n = 7 (M3).
2 At w1500 two recordings (patient 3 and 8) failed, because of difficulties in positioning the electrodes.
3 At M3 two patients refused pH-metry (patient 4 and 9). Recording was incomplete in one patient (patient 1).
4 P = 0.028, M3 vs pre-tx.
5 P < 0.05, d300 vs pre-tx.
6 P < 0.01, d300 vs pre-tx.

During the day the effect of octreotide on gastric acid secretion was mainly due to a reduction in meal-stimulated intragastric acidity (Table 4). This was significant at d300 and just failed to reach significance at M3 (P=0.027, pre-tx vs M3, n=7). Changes in fasting and preprandial acidity (before breakfast and dinner) were not significant. (Breakfast was served at 1000 h and lunch at 1200 h. Hence, there was no fasting preprandial time period before lunch).

Gastric mucosal histology

The histopathological Sidney scores for antrum and body mucosa are given in Table 5. Before therapy, gastritis (moderate to marked inflammatory infiltrates) was present in the four patients with H. pylori infection. None or only mild infiltration was seen in the other patients (except patient 8, who had moderate lymphoplasmacellular infiltration). Comparison of histopathological results of patients with gastroscopic evaluation before octreotide therapy and after 3 months of therapy (n=8) showed only minor variations in the activity score. The mean score for chronicity and atrophy in the antral mucosa, and for activity and atrophy in the body mucosa increased slightly after 3 months. Four of the six
H. pylori-negative patients had a repeat gastroscopy at M3. None of them had acquired new H. pylori infection. Histological and serological evaluation of H. pylori gave concordant results in all patients.

Discussion

Gastrin

Our results confirm that octreotide decreases serum gastrin (5–7). The almost maximal effect at the lowest dose used (300 µg/day) is in accordance with the near-maximal inhibition of gastrin secretion already at a dose of 75 µg/day in healthy normogastrinemic subjects (17). However, in contrast with the conclusion of a diminishing effect of octreotide on gastrin secretion drawn from short-term (1 week) treatment (17), our results show persistence of the suppressive effect during more prolonged administration. The return to pre-tx concentrations at M3 after its initial suppression must be interpreted taking into consideration the elevated pH at this time. Reduced intragastric acidity is a potent stimulus to gastrin secretion (26). In the presence of an
elevated pH, gastrin would therefore be expected to rise to higher than basal concentrations (28). In our patients, gastrin did not increase above pre-tx values, despite a substantial reduction in intragastric acidity. Thus the inhibitory effect of octreotide on gastrin secretion was at least partially preserved and the final gastrin concentration was determined by both the strong stimulation by the increased intragastric pH and the counteracting suppressive effect of octreotide. We have previously demonstrated that this inhibition of gastrin secretion persists during long-term treatment (several years) in acromegalic patients (18). As gastrin is an important trophic factor in the gastric mucosa (27), long-term disturbance of its physiological secretion could adversely affect mucosal morphology.

### Intragastric acidity

The mean pH value had increased greatly on the first day of octreotide therapy, although gastrin, which directly and indirectly accounts for up to 90% of stimulated gastric acid secretion (28), was only modestly reduced at this time. Other effects of octreotide on intragastric acidity are therefore likely to play a role. They probably include somatostatin receptor subtype-2 (SSTR-2)-mediated inhibition of histamine release from the enterochromaffin-like cells (ECL cells) (28–32) and/or a direct inhibition of the acid-secreting parietal cells (33–35). Interestingly, intragastric acidity was quickly restored, as previously observed by Londong et al. (17), despite an increase in the octreotide dose and in the presence of a continuously low gastrin concentration. The reason for the differing responses to ongoing octreotide therapy at this stage, i.e. resumption of acid secretion on the one hand and persistent suppression of gastrin secretion on the other, is not clear. Possible explanations include a difference in the somatostatin receptor population (although the SSTR-2 subtype seems to be mainly responsible for inhibition of both gastrin and acid secretion (30, 36)) and/or different intracellular effector pathways of the gastrin and ECL/parietal cells. Compensatory neuronal (muscarinic, β-adrenergic) stimulation of the ECL cells (29) may also be involved.

After 3 months of high-dose octreotide therapy, the initial recovery of acidity was not sustained and the intragastric pH was again higher than before treatment. Thus the final permanent suppression of gastric acidity (18) begins after only a few weeks of treatment. The restoration of intragastric acidity after 1
week of low-dose treatment described by Londoño et al. (17) is apparently only a temporary phenomenon. Later, a direct antiproliferative effect of octreotide on the gastric mucosa (as documented for somatostatin-14 in the rat (27), as well as a diminished trophic effect of gastrin may become effective. This is in keeping with the reduction in the volume and density of endocrine cells (mostly ECL cells) in the body mucosa (by 43 and 21% respectively) found in hypergastrinemic patients after 6 months of octreotide therapy (37).

The loss of transient nocturnal pH peaks (38, 39) is probably an indirect effect of octreotide therapy. These intermittent increases in gastric pH are attributed, at least in part, to gastroduodenal bile reflux associated with migrating motor complexes, which are more frequent during the night (40). Their disappearance may therefore be due to reduced alkaline content of the duodenal fluid and gastroduodenal reflux, in turn caused by octreotide-induced inhibition of bile secretion, gallbladder contractility and gastrointestinal motility (6, 7, 41).

Gastric mucosal histology

Only minimal changes in the gastritis scores were seen in our patients. We have shown previously that long-term (several years) octreotide treatment of acromegalic patients carries a risk of chronic active gastritis, although its incidence is a matter of discussion (14–16). Both a direct antiproliferative effect (27) of octreotide and inhibition of trophic factors (gastrin, histamine) (36, 42) could weaken the physiological gastric mucosal regeneration. On the other hand, octreotide-induced GH inhibition may diminish the risk of gastrointestinal malignancy in acromegaly (19, 20). In any case, our observations in this small sample of patients suggest that short-term (preoperative) octreotide treatment, in contrast with long-term (several years) treatment, is probably not a risk factor for permanent gastric mucosal morphological changes.

A high octreotide dose (1500 μg/day) was chosen in the present investigation in order to offer the patients a maximal preoperative effect on their GH concentration and tumor volume. We have previously shown that 1500 μg octreotide/day is more effective in some patients in reducing both GH concentration and tumor volume than either 300 or 600 μg/day (1, 3). Whether a lower dose, 3×100 μg octreotide/day for example, throughout would cause the same or smaller alterations in gastric mucosal function remains to be investigated.

Taken together, our results suggest a triphasic sequence of events in gastric mucosal function during the onset of octreotide therapy: (1) initially both gastrin and gastric acid secretion are reduced; (2) gastric acid secretion recovers quickly, but temporarily, although gastrin secretion is still inhibited; (3) finally, gastric acid secretion diminishes again permanently, although gastrin has now been restored to a ‘normal’ concentration, which, however, is inadequately low for the elevated intragastric pH. This new steady state seems to persist, at least for several years, during ongoing therapy (14).

We conclude that 3 months of preoperative octreotide therapy in this small sample carried no apparent risk of gastritis. However, gastric mucosal function was profoundly disturbed. These functional changes are potentially conducive to chronic active gastritis. We suggest that patients who need more prolonged therapy be screened for additional risk factors of chronic atrophic gastritis, such as H. pylori infection or parietal cell antibodies.

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