

# Octreotide in gastrointestinal motility disorders

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## Abstract

The effects of octreotide on six normal subjects and five patients with scleroderma were investigated. Changes in intestinal motility and in plasma motilin were examined after a single injection of octreotide. Octreotide stimulated intense intestinal motor activity in normal subjects. Motility patterns in the scleroderma patients were chaotic and non-propagative, but, after octreotide was given, became well coordinated, aborally directed, and nearly as intense as in normal volunteers. Clinical responses and changes in breath hydrogen were also evaluated in the five scleroderma patients who had further treatment with octreotide at a dose of 50 µg/day subcutaneously for three weeks. A reduction in symptoms of abdominal pain, nausea, vomiting, and bloating was seen. Additionally, there was an improvement in bacterial overgrowth as objectively measured by breath hydrogen testing. The effects of octreotide (100 µg/day subcutaneously) on the perception of rectal distension were investigated in a double blind, placebo controlled study in healthy volunteers. Octreotide was shown to reduce the perception of rectal distension without affecting motor pathways or local rectal reflexes. This enhanced tolerance to volume distension seems to result from inhibition of sensory afferent pathways as shown by electroencephalographic studies showing diminished evoked spinal and cortical potentials after octreotide. In irritable bowel syndrome patients with rectal urgency, octreotide reduces rectal pressures and perception after rectal distension to near normal values.

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Somatostatin has variable effects on motor activity of the gastrointestinal tract depending on the physiological state and region of the gastrointestinal tract studied. In the stomach, somatostatin inhibits the normal occurrence of cyclic interdigestive and fed motor activities.<sup>1</sup> In the intestine, somatostatin initiates ectopic fronts under basal conditions<sup>2</sup> but inhibits fed motility.

In normal subjects, somatostatin initiates a propagative pattern of motor stimulants in the duodenum, with a shortened cycle length of 40 minutes.<sup>3</sup> The long acting somatostatin analogue, octreotide, used in the treatment of endocrine tumours, evokes a similar intestinal pattern of contraction in dogs.<sup>4</sup> Therefore octreotide may be potentially useful in the treatment of small bowel dysmotility.

## Intestinal effects of octreotide in scleroderma

About 50% of patients with scleroderma have small bowel dysfunction.<sup>5</sup> In such patients, manometry shows patterns (known as the migrating motor complex) in the small bowel during fasting<sup>6</sup> and this may be clinically manifested as intestinal pseudo-obstruction and bacterial overgrowth. These problems are difficult to treat because standard stimulatory prokinetic agents are not effective in scleroderma.<sup>6</sup> We therefore recently undertook a study to determine the effects of octreotide in six normal subjects and in five patients with scleroderma who had abdominal pain, nausea, bloating, and a change in intestinal contractility.<sup>7</sup> We examined the changes in intestinal motility and in plasma motilin, a gastrointestinal hormone that stimulates intestinal motor activity, after single injections of octreotide (10 µg subcutaneously for normal subjects and 100 µg subcutaneously for scleroderma patients). We also studied the clinical responses and changes in breath hydrogen excretion (as a measure of intestinal bacterial overgrowth) in the five patients with scleroderma who were additionally treated with octreotide for three weeks at a dose of 50 µg/day subcutaneously. The diagnosis of scleroderma was made according to the criteria developed by the Subcommittee of Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee.

## SHORT TERM EFFECTS OF OCTREOTIDE ON INTESTINAL MOTILITY

Normal subjects showed propagative intestinal patterns during fasting with mean (SD) 1.5 (1.0) phase III complexes occurring every three hours (Fig 1). In contrast, none of the patients with scleroderma with pseudo-obstruction and bacterial overgrowth had any spontaneous duodenal phase III activity (Fig 1). Octreotide induced propagative phase III activity originated in the duodenum in all the normal subjects, whereas gastric phase III activity was suppressed. Duodenal phase III complexes evoked by octreotide were more frequent than spontaneous complexes. The normal subjects had 1.5 (1.0) phase III complexes during the three hours of basal recording and 4.1 (1.1) complexes during the three hours after octreotide was given, or roughly one complex every 40 minutes ( $p=0.012$ ). The octreotide evoked motor patterns consisted of alternating phase I and phase III activity, with noticeable reduction in the duration of phase II activity. The responses to octreotide in the patients with scleroderma were similar: octreotide increased the number of phase III complexes

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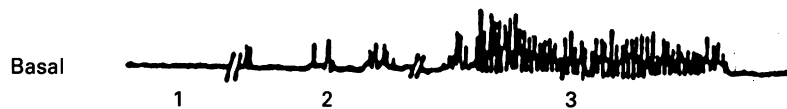
from 0 to 3.6 (2.3) per three hours, which is similar to the responses seen in the normal subjects. These complexes propagated at the same velocity and had two thirds the amplitude of the spontaneous complexes in normal subjects.

In normal subjects, before octreotide, plasma motilin concentration mean (SD) was 92 (27) pmol/litre in phase I, rising to 112 pmol/litre in phase III ( $p=0.05$ ). The phase III complexes evoked by octreotide were associated with a decrease in concentration to 57 (16) pmol/litre ( $p=0.006$  compared with phase I). Patients with scleroderma had persistently higher concentrations of plasma motilin (229 (74) pmol/litre,  $p=0.002$  compared with phase I normal subjects before octreotide). As in normal subjects, this was decreased by octreotide to a value of 141 (76) pmol/litre. These results suggest that the cycling of motilin is not necessary for octreotide induced complexes.

#### BREATH HYDROGEN EXCRETION AND GASTROINTESTINAL SYMPTOMS AFTER LONGTERM TREATMENT WITH OCTREOTIDE

Breath hydrogen excretion was assessed in the patients with scleroderma before and after three weeks of treatment with octreotide (50  $\mu\text{g}$  subcutaneously at bedtime), to provide an objective measurement of the presence and extent of bacterial overgrowth. Treatment with octreotide reduced breath hydrogen excretion while the patients were fasting from mean (SD) 25 (5) to 4 (2) ppm ( $p=0.001$ ) and breath

#### Normal subject



#### Patient with scleroderma



Figure 1: Intestinal manometric tracings in a normal subject and a patient with scleroderma. In the normal subject, the tracing shows a cyclic progression from the motor quiescence of phase 1 through the irregular activity of phase 2 to the intense phasic activity of phase 3. Octreotide (10  $\mu\text{g}$ ) stimulated intestinal phase 3 activity that was qualitatively similar to spontaneous phase 3 activity. In the patient with scleroderma with pseudo-obstruction, the tracing shows the absence of normal migrating complex cycling and, after octreotide (100  $\mu\text{g}$ ), intestinal phase 3 activity qualitatively similar to that in normal subjects. Reproduced by kind permission of the *N Engl J Med* 1991; 325: 1461-7.

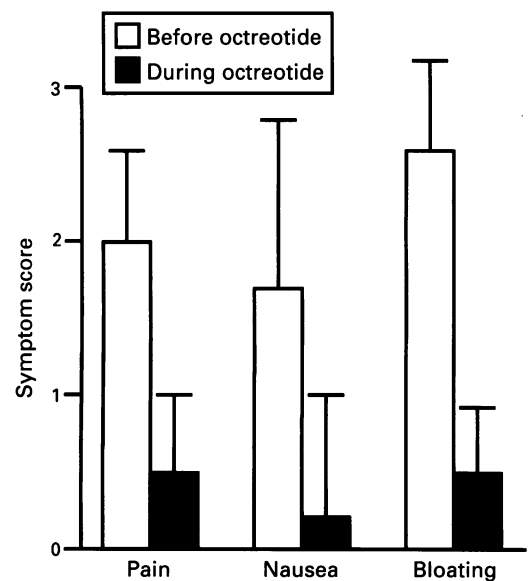


Figure 2: Effect of three weeks of treatment with octreotide (50  $\mu\text{g}$  every evening) in patients with scleroderma. There is a significant decrease in the mean (SD) daily symptom scores for abdominal pain, nausea, and bloating during treatment with octreotide ( $p \leq 0.05$ ). Reproduced by the kind permission of the *N Engl J Med* 1991; 325: 1461-7.

hydrogen excretion after ingesting 50 g of glucose from 46 (24) to 8 (7) ppm ( $p=0.015$ ). After treatment none of the patients had increased breath hydrogen excretion while fasting, and only one of five had a breath hydrogen increase of more than 15 ppm at that time. These results suggest substantial improvement in intestinal bacterial overgrowth in all patients.

Symptoms consistent with intestinal bacterial overgrowth and pseudo-obstruction were compared before and during the last seven days of the three week period of treatment with octreotide. The mean (SD) daily symptom scores for abdominal pain decreased from 2.0 (0.6) to 0.5 (0.5) during treatment ( $p=0.002$ ). Similarly, the symptom scores for nausea decreased from 1.7 (1.1) to 0.2 (0.2) ( $p=0.05$ ) and for bloating from 2.6 (0.6) to 0.5 (0.4) ( $p=0.003$ ) (Fig 2). The number of episodes of emesis decreased from 3.7 (2.9) to 0.1 (0.2) per week ( $p=0.05$ ). Finally there was no change in patients' weight before and during octreotide treatment.

#### SUMMARY

Short term treatment with octreotide stimulated propagative intestinal phase III like activity in patients with pseudo-obstruction secondary to scleroderma through motilin independent pathways. Treatment with octreotide for three weeks reversed abdominal breath hydrogen excretion and improved symptoms in patients with bacterial overgrowth. These data suggest that octreotide may be useful for the treatment of intestinal dysmotility in patients with scleroderma.

#### Antinociceptive activity of somatostatin

Somatostatin has antinociceptive activity in human and animal models of pain. Epidermal somatostatin infusion relieves intraoperative

and postoperative pain in patients who have had abdominal surgery.<sup>8</sup> Intraventricular somatostatin relieves intractable pain from disseminated malignancy.<sup>9-11</sup> In cats, perfusion of the dorsal surface of the spinal cord with somatostatin reduces neural responses to noxious heat stimulation of the extremities.<sup>12</sup>

The effects of somatostatin on sensory responses to visceral stimulation, however, are unexplored. In the following study we evaluated whether the somatostatin analogue, octreotide, inhibits afferent pathways that mediate perception of rectal pressure in healthy subjects<sup>13</sup> and patients with irritable bowel syndrome.<sup>14</sup>

#### RECTAL AFFERENT INHIBITION BY OCTREOTIDE IN HEALTHY SUBJECTS

In normal subjects, progressive rectal distension initially leads to perception of pressure, followed by faecal urgency, and then pain. The effects of octreotide on perception of rectal distension were studied in a double blind, placebo controlled fashion in eight healthy volunteers. After octreotide administration (100 µg subcutaneously), threshold perception, pressure, urgency, and maximal tolerated volume were reported at mean (SD) 62 (4), 185 (11), 269 (17), and 362 (25) ml, which were greater than after placebo (25 (4), 95 (9), 153 (10), and 211 (13) ml,  $p < 0.01$ ). Rectal pressures, which increased from 9.2 (1.2) mm Hg at 30 ml to 20.2 (1.7) mm Hg at 180 ml after placebo, were not modified by octreotide; this shows a lack of effect on rectal resistance. In addition to enhancing volumetric tolerance, however, maximally tolerated pressures were increased to 42.4 (5.1) mm Hg by octreotide ( $p < 0.01$ ). Octreotide increased phasic rectal contractions but did not change anal pressures or block the rectoanal inhibitory reflex, confirming that local rectal reflex arcs are unaffected. Perception of thermal or electrical cutaneous stimulation was unaffected by octreotide, showing selectivity for visceral afferent pathways. These studies show that octreotide reduces sensation of rectal distension by inhibition of visceral afferent pathways. In contrast, afferent pathways participating in local reflexes and cutaneous perception are not inhibited by octreotide.

#### RECTAL AFFERENT INHIBITION BY OCTREOTIDE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Patients with irritable bowel syndrome (IBS) often present with abdominal pain, refractory to treatment. The mainstays of treatment in these subjects have been drugs designed to reduce spastic motor activity, even though many of these subjects have no pathognomonic disturbances of visceral motor activity.<sup>15</sup> It has been shown that patients with IBS exhibit a heightened sensitivity to rectal distension.<sup>16</sup> We therefore evaluated the effects of octreotide on afferent pathways that mediate perception of rectal pressure and pain in patients with IBS.<sup>14</sup> Octreotide (100 µg subcutaneously)

and placebo were injected in a double blind fashion in five diarrhoea predominant irritable bowel patients and eight healthy subjects. Rectal balloons measured volumes that evoked increasing levels of perception and intrarectal pressures. After placebo, threshold perception, pressure urgency, and maximal tolerated volume were reported at mean (SD) 14 (5), 49 (13), 71 (12), and 104 (16) ml by the IBS patients, values less than in healthy subjects (25 (4), 95 (9), 153 (10), and 211 (13) ml,  $p < 0.02$ ).

With octreotide, these sensations were perceived by the IBS patients at higher volumes (37 (12), 92 (21), 159 (25), and 203 (31) ml), which were similar to responses in healthy subjects. We have shown that octreotide does not affect rectal pressure-volume relations in healthy subjects. IBS patients exhibited higher rectal pressures at each volume and showed a trend to higher rectal resistance compared with healthy subjects after placebo, abnormalities that returned to normal with octreotide. Similar to the findings in healthy subjects, octreotide did not block the rectoanal inhibitory reflex, confirming a lack of effect on local rectal reflex arcs. Therefore, as with healthy subjects, IBS patients with diarrhoea experience reduced perception of rectal distension after octreotide. Octreotide also reduces raised rectal pressures in IBS patients, in contrast with healthy subjects. Thus octreotide shows potential therapeutic benefit in IBS by effects on visceral afferent pathways and rectal wall stiffness.

#### EVIDENCE THAT OCTREOTIDE REDUCES PERCEPTION OF RECTAL DISTENSION BY SPECIFIC INHIBITION OF SPINAL AFFERENT PATHWAYS

The site of the inhibitory effects of somatostatin on perception of visceral distension is unknown. Investigations in animal models suggest somatostatin may act at multiple sites. Superfusion of somatostatin in the spinal cord of cats reduces action potentials from dorsal horn neurons in response to thermal stimuli.<sup>12</sup> Somatostatin depresses the excitability of neurons in laminae I, II, and IV of the dorsal horn of the cat.<sup>17</sup> Somatostatin reduces neural activity in spinal cord neurons and dorsal root ganglia neurons by inhibitory effects on N-type calcium channels.<sup>18,19</sup> To localise the site of action in vivo, we compared perception of rectal electrical stimulation to cerebral and spinal evoked potential recordings (EP) in five healthy subjects 60 minutes after double blind octreotide (100 µg subcutaneously) *v* placebo injection.<sup>20</sup> Rectal bipolar electrodes were placed after enema preparations. Square wave impulses (0.5 ms duration at random frequencies, mean = 0.5 Hz, given before and 60 minutes after double blind octreotide or placebo) were delivered at voltages 50% above those that elicit threshold perception. Perception of electrical stimulation was recorded by a visual analogue scale (1 = no sensation, 10 = severe pain). Octreotide reduced perception scores from 8.1 (1.2) to

4.7 (1.1) whereas placebo had no effect. Thus octreotide has inhibitory effects on pathways mediating perception of rectal electrical stimulation. Cerebral EPs (centred at Cz) showed an initial negative peak ( $N_1$ , latency=100 ms) followed by a positive peak ( $P_1$ , latency=250 ms). Octreotide had no effect on latencies, but maximal peak to peak amplitudes were reduced by 35 (12)%, showing an inhibition of afferent pathways that project from the rectum to the cerebrum. Spinal EPs (centred at  $S_1$ ) assessed if this inhibition localised to pathways that project from the rectum to the spinal cord. Spinal EPs had an initial negative peak ( $N_1$ , latency=7 ms), followed by a positive peak ( $P_1$ , latency=10 ms) and a second negative peak ( $N_2$ , latency=13 ms). As with cerebral EPs, octreotide had no effect on spinal EPs, but reduced the maximal peak to peak signal amplitude by 50 (21)%, confirming that inhibition occurs at the level of spinal afferent pathways. These studies therefore showed that octreotide reduces perception of rectal electrical stimulation, which is associated with inhibition of cerebral and spinal evoked potential amplitude. Octreotide reduces rectal sensation by effects on spinal afferent pathways. These findings suggest a possible role for the somatostatin analogue in the treatment of conditions with enhanced sensory perception such as IBS.

### Conclusion

Our studies show that octreotide may be a novel prokinetic agent for the treatment of pseudo-obstruction in scleroderma. Octreotide stimulates intense propagative intestinal motor activity in normal subjects. Small intestinal motility patterns in the scleroderma patients before octreotide are chaotic and non-propagative; after short term octreotide administration, intestinal motility is well coordinated, aborally directed, and nearly as intense as in normal volunteers. Longterm subcutaneous administration of octreotide results in reduction in symptoms of nausea, vomiting, bloating, and abdominal pain and improvement in bacterial overgrowth as objectively measured by hydrogen breath testing. These findings suggest that octreotide may be a novel motor stimulatory agent for the treatment of intestinal motility disturbances in scleroderma patients. In addition, octreotide also reduces the perception of rectal distension without affecting motor pathways or local rectal reflexes. This enhanced tolerance to volume distension seems to result from inhibition of sensory

afferent pathways as shown by electroencephalographic studies showing diminished evoked spinal and cortical potentials after octreotide. In irritable bowel syndrome patients with rectal urgency, octreotide reduces rectal pressures and perception after rectal distension to near normal values. Thus octreotide may have therapeutic benefits in irritable bowel patients.

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