Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome

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SUMMARY The effect of a long acting somatostatin analogue SMS 201-995 on stomal effluents in patients with severe short bowel syndrome was investigated in a double blind placebo controlled balance study. Six patients, five with Crohn's disease and one with radiation enteropathy were studied. Five patients had a jejunostomy and one an ileostomy. The patients had a normal food intake, but because of severe malabsorption had received home parenteral nutrition for several years. Faecal mass was reduced (p<0.005) and intestinal net sodium absorption was increased (p<0.005) by intravenous infusion of SMS 25 µg/h. Net absorption of potassium, calcium, magnesium, phosphate, zinc, nitrogen and fat was not influenced. Subcutaneous injections of 50 µg SMS every 12 hours had a similar effect on net intestinal absorption of sodium and water. Four patients continued with a five to six months open follow up study when subcutaneous SMS in the same dose was administered by the patients at home. The effect on faecal sodium loss persisted, but in one patient faecal mass gradually increased and finally exceeded pretreatment values. SMS may decrease net absorption of water and sodium following reduced secretion of digestive juices rather than by increasing absorptive capacity. SMS may be useful as an antidiarrhoeal drug in patients with high output jejuno- or ileostomies, but in patients who need permanent parenteral nutrition the effect is too small to significantly alter management.

Extensively small bowel resected patients with ileo- or jejunostomy suffer from excessive losses of sodium and water in the stomal effluents. It is possible that the large stomal output of sodium and water secondarily reduces intestinal absorption of other nutrients by flushing them out. Some of the patients need permanent parenteral nutrition, especially parenteral saline supply to avoid life threatening sodium depletion and dehydration. These patients are trained to administer parenteral nutrition at home. This is, however, expensive, time consuming, and hazardous, and it makes heavy demands on the patient and often also on the family. It would therefore be of major clinical importance to find a way to reduce the stomal effluents, at best to increase the intestinal net absorption enough to render parenteral supply superfluous.

Mineralocorticoids increase the colonic absorption of sodium and water, but have no effect on the proximal small intestine. Cimetidine reduces stool mass and faecal sodium loss in patients with jejunostomy, presumably by reducing the secretion of gastric juice which often is increased in short bowel patients. In only half of the patients is the effect great enough to be of clinical benefit, however, and still not great enough to make parenteral saline unnecessary.

Somatostatin suppresses many of the gut peptides implicated in the control of secretory and motor activity of the gastrointestinal tract. It has been shown to reduce faecal losses in a few patients with secretory diarrhoea and short bowel syndrome. The therapeutical applicability of somatostatin is, however, limited by its short half life (two to three

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minutes). Therefore longer acting analogues have been developed. Such a drug (SMS 201-995, Sandoz Ltd) has been shown to control diarrhoea in a single patient with high output ileostomy.6

The purpose of the present study was to evaluate the effect of SMS 201-995 on intestinal net absorption of water, minerals, nitrogen, and fat in a group of patients on permanent parenteral nutrition because of high output ileo- or jejunostomies.

Methods

Patients

Six patients, four women and two men, with a median age of 40 years (range 28–71), were studied (Table 1). Five patients had Crohn’s disease, one had radiation enteropathy. One patient with Crohn’s disease had a resection of only 30 cm terminal ileum, but a functional short bowel syndrome and had an ileostomy. The remaining patients had jejunostomies with a length of the remaining small intestine between 40 and 225 cm (median, 110 cm) measured peroperatively from the ligament of Treitz to the stoma. The patients had a normal food intake (Table 2), but because of severe malabsorption they had required daily parenteral nutritional supplies including minerals and vitamins administered at home for 14 to 101 months (median, 35 months). The patients were in a steady state, ambulatory and well at the time of the study with stable oral and parenteral intakes, stable body weight, and normal blood biochemistry.

The study was in accordance with the Helsinki II declaration and registered with the local ethical committee. All patients gave their informed consent.

Experimental procedure

The patients were placed on a constant diet for 12 days with a fixed daily amount of all nutrients including sodium and water. To ensure steady state conditions the diet was composed in accordance with the individual patient’s habitual food intake, and the patients continued with their usual daily parenteral programme (Table 2). The diet was duplicated; one for consumption and one for analysis.

After a basal period of two days the patients were randomly allocated to intravenous infusion of either placebo or SMS for two days and vice versa for the next two days, each patient serving as his/her own control. The dose of SMS was 25 μg/h. SMS and placebo were dissolved in 154 mM NaCl and 0-2% albumin. Albumin was added to avoid adherence of SMS to the plastic tubing of the administration set, a phenomenon well known for some polypeptide hormones. After a new basal period of two days the patients were once again randomly allocated to subcutaneous administration of either placebo or SMS for two days and vice versa for the next two days. SMS was given in a dose of 50 μg every 12 hours in this part of the study. Stools and urine were collected daily.

Blood glucose was measured three times per day. Blood haemoglobin, plasma sodium, potassium, protein, carbamide, creatinine, and bicarbonate were determined on day 1, 3, 5, 7, 9, 11, and 13 of the study. Serum calcium, magnesium, phosphate, zinc, bilirubin, alkaline phosphatase, ALAT, factor II, VII, X, leucocyte, and thrombocyte count were measured on day 1 and 13.

After the balance study five patients continued with self administration at home of 50 μg SMS subcutaneously twice per day for four to 28 weeks (median 22 weeks). One patient, who developed an episode of intestinal obstruction during the balance study (vide infra), did not participate in this part of the investigation. One patient stopped after four weeks. The reason was that she lived far from the hospital and therefore was unable to attend the outpatient clinic at two week intervals as planned. One patient (case 1) took double doses of SMS: 100 μg twice per day from the fifth to the 28th week. The patients continued their normal pre-examinatory habits, including food intake, parenteral programme and social life. A clinical check up was done at the outpatient clinic every two to four weeks, when 24 hour samples of urine and stools were analysed.

Table 1 Clinical details in six patients with high output ileo- or jejunostomies

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Primary disease</th>
<th>Remaining small intestine (cm)</th>
<th>Duration of HPN (mo)</th>
<th>Stool mass* (g/24 h)</th>
<th>Stool sodium* (mmol/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RE</td>
<td>40</td>
<td>21</td>
<td>8210</td>
<td>286</td>
</tr>
<tr>
<td>2</td>
<td>CD</td>
<td>100</td>
<td>49</td>
<td>8125</td>
<td>691</td>
</tr>
<tr>
<td>3</td>
<td>CD</td>
<td>110</td>
<td>85</td>
<td>2935</td>
<td>262</td>
</tr>
<tr>
<td>4</td>
<td>CD</td>
<td>150</td>
<td>101</td>
<td>4645</td>
<td>399</td>
</tr>
<tr>
<td>5</td>
<td>CD</td>
<td>225</td>
<td>18</td>
<td>2320</td>
<td>293</td>
</tr>
<tr>
<td>6</td>
<td>CD</td>
<td>All – 30 cm</td>
<td>14</td>
<td>3270</td>
<td>144</td>
</tr>
</tbody>
</table>

CD=Crohn’s disease; RE=Radiation enteropathy; HPN=Home parenteral nutrition. *Basal period.

Table 2 Daily oral parenteral intakes

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Water (ml)</th>
<th>Sodium (mmol)</th>
<th>Protein/aa (g)</th>
<th>Energy (kJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5139/7500</td>
<td>126/448</td>
<td>50/100</td>
<td>6294/11130</td>
</tr>
<tr>
<td>2</td>
<td>5137/4500</td>
<td>211/294</td>
<td>85/100</td>
<td>9361/7710</td>
</tr>
<tr>
<td>3</td>
<td>1778/4000</td>
<td>120/304</td>
<td>61/66</td>
<td>8100/8050</td>
</tr>
<tr>
<td>4</td>
<td>3185/5250</td>
<td>121/458</td>
<td>84/66</td>
<td>8813/9100</td>
</tr>
<tr>
<td>5</td>
<td>3434/4500</td>
<td>213/448</td>
<td>117/50</td>
<td>13698/3910</td>
</tr>
<tr>
<td>6</td>
<td>4206/4150</td>
<td>82/294</td>
<td>46/100</td>
<td>4028/9200</td>
</tr>
</tbody>
</table>
ANALYTICAL METHODS
Blood analyses were performed by routine methods in the department of clinical chemistry, Rigshospitalet.
Calcium, magnesium and zinc in diet, faeces and urine were measured by atomic absorption spectrophotometry, sodium and potassium by flame photometry.
Phosphorus content of diet, faeces, and urine was determined spectrophotometrically, for diet and faeces after dry ashing.
Nitrogen analyses of diet, faeces and urine were carried out by the Kjeldahl technique. Fat content of diet and faeces was determined by van de Kamer’s method.
Intake and excretions in the different periods (placebo v SMS) were calculated as the mean of two days.

STATISTICAL ANALYSIS
Data were compared by Student’s t test for paired comparison. p<0.05 was considered significant.

Results
Intestinal net absorption of water was determined as the difference between dietary mass (including liquids) and faecal mass=net mass absorption, which implies some overestimation of the true net water absorption.

During the placebo periods four of the six patients had an intestinal net loss of water, and all six had a net loss of sodium (Figs. 1, 2).

Infusion of SMS 25 µg/h caused a significant increase of net mass absorption as well as of net absorption of sodium (Fig. 1). The increase of net mass absorption ranged from 347 to 1853 g/24 h, median 1124 g/24 h. The increase of net sodium absorption ranged from 52 to 191 mmol/24 h, median 126 mmol/24 h. Only two of the four patients with an initial faecal net mass loss obtained a positive net mass absorption (and less than 1000 g/24 h) during SMS treatment, however, and only one patient obtained a positive net sodium absorption of only 9 mmol/24 h. In no patient, thus, seemed the reduction of stomal losses large enough to make parenteral sodium supply superfluous. Net absorption of potassium did not change significantly (Fig. 1). There was no significant change of net absorption of calcium, magnesium, phosphate, zinc, nitrogen or fat during infusion of SMS (Table 3).

Subcutaneous injection of 50 µg SMS every 12 h caused a similar increase of net mass absorption and net absorption of sodium (Fig. 2). In patient no 5 stomal effluents gradually decreased to almost nil during the first day of subcutaneous treatment with SMS. An abdominal roentgenogram suggested paralytic ileus. Several hours later he developed abdominal colic, vomiting and an abdominal roentgenogram indicating intestinal obstruction so SMS was withdrawn. A barium enema suggested kinking of the bowel 20 cm from the stoma. The small bowel obstruction resolved within three days upon conservative treatment. Because of intestinal blockade he showed very large ‘net absorption’ of all elements, which partly reflected intestinal stagnation rather than true absorption. He therefore was excluded from this part of the balance study. The increase of mass absorption in the remaining five patients ranged from 637 to 2108 g/24 h, median 1370 g/24 h, and the increase of sodium absorption from 16 to 142 mmol/24 h, median 115 mmol/24 h. Net potassium absorption also increased significantly (Fig. 2), however, only 2 to 20 mmol/24 h, median 11 mmol/24 h. Net absorption of calcium, magnesium, phosphate, zinc, nitrogen and fat remained unchanged (Table 4).

Blood glucose remained within normal ranges during SMS therapy. Neither did the other blood variables change consistently.

Four patients continued on open treatment with 50 µg SMS twice per day for 21 to 28 weeks. In three patients faecal mass remained below basal values, but in patient no 1 with the 40 cm jejunal remnant, faecal mass increased gradually, exceeding basal values despite increasing the dose of SMS to 100 µg twice per day. Stomal sodium excretion persisted between 50 to 90% of the basal loss (Fig. 3).

Except for the one case of intestinal obstruction no side effects were recorded in any of the series.

Discussion
Somatostatin exerts a wide range of physiological effects on the gastrointestinal tract. It reduces splanchnic blood flow. It inhibits exocrine secretions from the stomach, pancreas, and small intestine. It impairs gastrointestinal motility, and it reduces intestinal absorption of all kinds of nutrients.

SMS 201-995 is a long acting octapeptide (t½=one to two hours) compared with the endogenous somatostatin (t½=two to three min). SMS possesses the same spectrum of effects as somatostatin but is more potent.

We found, that SMS significantly reduces faecal loss of water and sodium in patients with high output jejuno- or ileostomies in both continuous infusions and two daily single injections. This is in accordance with previous findings in a single patient. In contrast, SMS did not influence net absorption of potassium, calcium, magnesium, zinc, and phosphate, even if the
Table 3  Mean daily gastrointestinal net absorption of calcium, magnesium, phosphate, zinc, nitrogen, and fat during continuous, intravenous infusion of SMS 201-995 25 μg/h for 48 hours

<table>
<thead>
<tr>
<th>Gastrointestinal net absorption/24 h</th>
<th>SMS 201-995 25 μg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium (mmol)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>-5.0–+6.9</td>
</tr>
<tr>
<td></td>
<td>-2.1–+3.3</td>
</tr>
<tr>
<td></td>
<td>-4.2–+16.5</td>
</tr>
<tr>
<td></td>
<td>-52–+98</td>
</tr>
<tr>
<td></td>
<td>-0.9–+10.2</td>
</tr>
<tr>
<td></td>
<td>+5–+105</td>
</tr>
</tbody>
</table>

Table 4  Mean daily gastrointestinal net absorption of calcium, magnesium, phosphate, zinc, nitrogen, and fat during treatment with SMS 50 μg subcutaneously every 12 h for 48 hours

<table>
<thead>
<tr>
<th>Gastrointestinal net absorption/24 h</th>
<th>SMS 201-995 50 μg sub every 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium (mmol)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>-8.8–0.5</td>
</tr>
<tr>
<td></td>
<td>-3.1–+2.0</td>
</tr>
<tr>
<td></td>
<td>-3.8–+14.8</td>
</tr>
<tr>
<td></td>
<td>-74–+22</td>
</tr>
<tr>
<td></td>
<td>-0.7–+5.3</td>
</tr>
<tr>
<td></td>
<td>+5–+47</td>
</tr>
</tbody>
</table>

Fig. 1  Mean daily gastrointestinal net absorption (oral intake − faecal loss) of water, sodium and potassium during continuous, intravenous infusion of SMS 201-995 25 μg/h for 48 hours.
Fig. 2  Mean daily gastrointestinal net absorption of water, sodium and potassium during treatment with SMS 50 μg subcutaneously every 12 h for 48 hours.

luminal concentrations increased after enhanced water absorption.

Net absorption of water and minerals in the intestine reflects a balance between absorption of the dietary intake and loss from the digestive juices. In bowel resected patients intestinal absorption depends on the extent and the integrity of the bowel remnant as well as on the intestinal transit time – that is, the contact time between the luminal content and the absorptive surface.

Perfusion studies have shown, that somatostatin and SMS have no effect on jejunal absorption of sodium and water. In contrast with the other minerals studied, the majority of luminal sodium derives from gastrointestinal and pancreaticobiliary secretions. It is therefore likely that the increased net absorption of water and sodium mainly reflects a decreased secretion of digestive juices. An increased absorption secondary to a prolongation of the transit time is presumably not of major importance, because per se that would result in an increased absorption of the other elements studied.

Cimetidine has been shown to reduce faecal losses of water and sodium in patients with high output jejunostomies. The reduction is, however, much smaller than that caused by SMS, presumably because cimetidine inhibits gastric secretion only, while SMS also causes a reduction of pancreatic and small intestinal secretions.

Somatostatin and SMS can decrease pancreatic secretion of enzymes by about 75%. In the present study net absorption of protein and fat, however, remained unchanged during SMS treatment. This is consistent with the findings, that pancreatic enzyme secretion has to be decreased by about 90% before significant maldigestion occurs.

In the basal/placebo periods subsequent to SMS administration stomal losses rapidly returned to basal values without exceeding these – that is, no rebound effect took place.

In the placebo periods four of six patients had a net water loss from the intestine and all six had a net loss of sodium. During SMS infusion faecal water and sodium loss diminished, but only one patient obtained a slight net gain of sodium. Although SMS reduced the need for parenteral saline corresponding to approximately 1 l isotonic saline per day, no patient was able to dispense completely with parenteral supply.

It can not be excluded, that the effect of SMS might have been greater if combined with a reduction of parenteral saline. It has been shown, that parenteral
saline infusions cause an increase of stomal water and sodium output in patients with ileostomy. The increase shown was, however, small, and saline infusions did not change stomal losses in ileostomy patients with part of the ileum resected.

The reduction of stool mass induced by SMS had obviously great psychological and social advantages in the daily lives of the patients, but because of the high cost of SMS (about £12 per day for a dose of 50 µg every 12 h) it will hardly win greater therapeutical application for these patients. It is, however, possible, that SMS in patients with lesser voluminous stomal effluents can reduce faecal water and sodium loss enough to ensure normal water and sodium balance. After the study some patients continued to take SMS prn before major social events when a temporary decrease of stomy output was desirable.

Subcutaneous injection of a total of 100 µg SMS per 24 hours had largely the same effect on intestinal net absorption of water and sodium as intravenous infusion of 600 µg SMS per 24 hours. It suggests that the maximum effect on net water and sodium transport is obtained by a dose of 100 µg SMS per 24 hours.

Somatostatin and SMS influence glucose metabolism by suppressing the secretion of insulin, glucagon and growth hormone, and it may induce glucose intolerance. In the present study blood glucose concentrations did not change significantly during SMS supply and did not exceed normal ranges.

One patient developed intestinal obstruction during administration of 50 µg SMS every 12 hours. It might be a coincidence, but the course of events suggested that SMS may have caused some intestinal dilatation which resulted in kinking of the bowel. No other side effects were recorded.

In the follow up treatment of four patients with 50 µg SMS twice daily faecal mass and sodium output were measured regularly. Both showed large variations, but faecal sodium persisted between 50 and 90% of the initial basal values, suggesting that no adaptation took place. In one patient with a very short intestinal remnant faecal mass, however, gradually increased, exceeding the initial values despite increasing the SMS dosing.

SMS 201-995 reduces faecal loss of water and sodium significantly in patients with high output jeuno- or ileostomies presumably by decreasing the secretion of digestive juices. In patients who require permanent parenteral supplementation the effect of SMS, however, is evaluated to be too small to render parenteral saline superfluous.

This work was supported by grants from the Foundation for Advancement of Medical Science, P Carl

Fig. 3  Stool mass and faecal sodium loss in per cent of basal values during longterm open follow-up treatment with SMS 50 µg subcutaneously every 12 h.
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References

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