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A pilot study of the effects of the somatostatin analog pasireotide in postoperative dumping syndrome

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Key Messages

- Somatostatin analogs (SA) are the most effective treatment modality for dumping syndrome.
- Currently available SA have suboptimal efficacy, possibly because of their limited affinity for the different types of somatostatin receptors.
- Pasireotide is a novel SA with high affinity for four of five known somatostatin receptors.
- We studied its effects on pathophysiological mechanisms underlying dumping syndrome in nine patients.
- Pasireotide treatment prevented hypoglycemia and the rise in pulse rate during an oral glucose challenged, slowed gastric emptying rate.
- We conclude that pasireotide has strong pharmacodynamics effects on relevant pathophysiological mechanisms in dumping syndrome.

Abstract

Background *Dumping syndrome is characterized by distinct pathophysiological features such as postprandial increase in hematocrit (HT) and pulse rate (PR) and delayed hypoglycemia (HG). Treatment is based on dietary measures and somatostatin analogs (SA), but current SAs have incomplete efficacy, possibly through limited affinity for various somatostatin receptor subtypes. We evaluated the effect of pasireotide, a novel SA with high affinity for 4/5 human somatostatin receptors, on pathophysiological events and symptoms in dumping.* ***Methods*** *Randomized double-blind placebo-controlled cross-over study of nine patients (six women, 47 ± 4 years) with postoperative dumping. Baseline measurements included oral glucose tolerance testing (OGTT), abdominal ultrasound, and dumping symptom severity score (DSSS). Patients were treated for 2 weeks with placebo or pasireotide 300 μg s.c. t.i.d. with a 1-week wash-out in a randomized fashion. On day 13 and 14 of each treatment OGTT, DSSS, and solid and liquid gastric emptying (GE) were obtained.* ***Key Results*** *Baseline OGTT was pathological in all patients based on PR (n = 5), HT (n = 1) or HG (n = 7). Compared to placebo, pasireotide suppressed the increase in PR (17.1 ± 2.8 vs 8.2 ± 3.5 bpm; $p < 0.05$) and late HG (nadir glycemia 55.6 ± 4.3 vs 83.3 ± 9.5 mg/dL; $p = 0.007$), increased peak glycemia (294.1 ± 33.3 vs 221.0 ± 23.1 mg/dL; $p = 0.001$) and delayed GE of solids (t1/2 83 ± 23 vs 43 ± 9 min; $p = 0.05$) and liquids (t1/2 70 ± 10 vs 40 ± 4 min, $p = 0.05$). The differences in DSSS did not reach statistical significance. Two patients dropped out because of adverse gastrointestinal events under pasireotide.* ***Conclusions & Inferences*** *Pasireotide affects pathophysiological features of both early and late dumping syndrome.*

Keywords *dumping syndrome, gastric emptying, glucose tolerance testing, pasireotide, randomized-controlled trial, somatostatin analog.*

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INTRODUCTION

Dumping syndrome is a well-established but under-recognized complication of gastric and esophageal surgery.[1] Although the clinical presentation may vary, dumping syndrome symptoms are traditionally subdivided into early and late dumping symptoms. Early dumping symptoms are attributed to the rapid delivery of osmotically active nutrient particles to the small intestine, which triggers a combination of gastrointestinal and vasomotor symptoms.[1] Hemoconcentration and a rise in plasma levels of several peptide hormones, including insulin, enteroglucagon, neurotensin, and vasoactive intestinal peptide, have been implicated in the pathogenesis of early dumping symptoms.[1–4] Late dumping symptoms typically occur 1–3 h postprandially and are attributed to reactive hypoglycemia.[1] Dumping syndrome is now a well-established complication of gastric and esophageal surgery, with estimated prevalences of up to 50% after esophagectomy or gastrostomy.[1,5] Dumping syndrome has also been reported after Nissen fundoplication in children and in adults.[6–8] More recently, bariatric surgery has become the principal cause of postoperative dumping symptoms.[1,9]

Diagnosing dumping syndrome is based on clinical suspicion, often with confirmation by a dumping provocative test.[1,10] Besides dietary measures, treatment is often based on the administration of somatostatin analogs (SA), which are the most effective treatment modality for dumping syndrome.[1,8,11] However, a subset of patients do not respond to currently available SA, and in the long term many patients discontinue therapy with SA.[1,8,12,13] In an early study of 20 patients treated with subcutaneous octreotide, treatment was stopped in 11 over a 36-month follow-up because of loss of efficacy or adverse effects.[12] The short-acting form of octreotide is less attractive for chronic use to patients due to the intensity of the administration schedule, but the depot long-acting release form seemed numerically less effective in two studies.[8,11] In a study of 34 patients initially treated with octreotide and with access to the long-acting release form, 16 patients interrupted treatment because of side effects or lack of efficacy.[13] Hence, a substantial unmet need persists in the medical treatment of dumping syndrome.

One reason for the incomplete therapeutic effects of currently available SA could be the limitation of their high affinity to only one type of somatostatin receptor, the sst2 receptor.[14] Pasireotide is a SA which exhibits a unique binding profile with high affinity for four of the five known human somatostatin receptors (sst1-5). Compared to octreotide, pasireotide has comparable affinity for the sst2 receptor, binds with a 30- to 40-fold higher affinity than octreotide to the sst1 and sst5 receptor subtypes and with a five-fold higher affinity to sst3.[14] Based on these receptor affinities, pasireotide is expected to cause a larger inhibition of hormone release in dumping syndrome.[15,16]

The aim of this study was to evaluate the therapeutic potential of pasireotide in patients with dumping syndrome. We therefore conducted in a mechanistic cross-over study with pasireotide and *placebo*.

MATERIALS AND METHODS

Study subjects

Consecutive eligible patients with symptoms suggestive of dumping syndrome and with objective evidence of dumping syndrome (see below) were recruited for this study. All patients underwent careful history taking and clinical examination, routine biochemistry, upper gastrointestinal endoscopy, abdominal ultrasound, barium x-ray of the upper abdominal tract, and an oral glucose tolerance test (OGTT). Patients were eligible for the study if they had a score of 10 or more on a dumping syndrome severity scale (see below) and objective evidence of dumping through either spontaneous hypoglycemia (HG) or a positive OGTT (see below), and when symptoms persisted in spite of dietary measures. Spontaneous HG refers to a glycemia level of <50 mg/dL measured outside of the setting of the OGTT, usually at the time of symptoms of drowsiness or decreased consciousness. Patients who had received SA during the last 12 weeks, or patients who had failed to respond to SA, were excluded from the study.

Questionnaires

No validated symptom score for dumping syndrome has been reported. On the basis of literature reports, we previously developed a dumping syndrome severity score (DSSS), which has previously been shown to be sensitive to therapeutic improvement with SA.[1,8] The patient was asked to grade the intensity (0–3; 0 = absent, 1 = mild, 2 = relevant, and 3 = severe, interfering with daily activities) of eight early dumping symptoms (within 1 h after food ingestion) and six late dumping symptoms (later than 1 h after food ingestion; Table 1). Quality of life was measured using the SF-36 questionnaire.[17] At the end of each treatment period, patients filled out a global assessment, where they used a 7-item scale (ranging from a lot worse to a lot better, with unchanged in the middle) to respond to the question 'How do you feel compared to your situation before starting the study?'.

Oral glucose tolerance testing

Oral glucose tolerance testing was performed as previously reported.[8] Patients drank 75 g of glucose and glycemia, insulinemia, glucagon plasma levels, pulse rate (PR), blood pressures, and hematocrit were measured at 0, 30, 60, 120, and 180 min after glucose ingestion. Throughout the test, subjects remained in a sitting position in a comfortable chair.

Table 1 Quality of life (SF-36) at baseline and during treatment with *placebo* or pasireotide. No significant differences were found

	Physical functioning	Role physical	Role emotional	Bodily pain	Social functioning	Mental health	Vitality	General health
Baseline	55.0 ± 8.5	25.0 ± 14.4	22.2 ± 18.4	25.4 ± 7.1	38.9 ± 10.5	44.4 ± 7.0	3.,9 ± 7.7	29.9 ± 7.6
Placebo	67.9 ± 10.7	57.1 ± 20.2	57.1 ± 20.2	35.6 ± 6.3	53.6 ± 10.1	57.7 ± 7.7	41.4 ± 9.8	33.1 ± 7.9
Pasireotide	58.8 ± 10.9	40.6 ± 17.6	37.5 ± 18.3	35.0 ± 6.4	43.8 ± 9.1	53.5 ± 6.8	41.3 ± 6.9	32.5 ± 6.3

Gastric emptying

Gastric emptying rates for solids and liquids were determined using the ^{14}C octanoic acid and ^{13}C glycin breath test, as previously reported.[8,18,19] The test meal (250 kcal) consisted of 60 g of white bread, an egg, the yolk of which was doped with 74 kBq of ^{14}C octanoid acid sodium salt (DuPont, NEN Research, Boston, MA, USA), and 300 mL of water in which 100 mg ^{13}C glycin (99% enrichment; Isotec, Miamisburg, OH, USA) was dissolved.

Study design

After obtaining informed consent, baseline OGTT was performed, and abdominal ultrasound was performed to rule out cholelithiasis, and patients filled out a baseline DSSS questionnaire. Next, patients were treated for 2 weeks with *placebo* or pasireotide 300 μg s.c. t.i.d. (Fig. 1). The best explored dose regimen for pasireotide is 600 μg b.i.d., in Cushing's disease.[20] Based on the need for t.i.d. administration (before each meal) in dumping syndrome, administration of 300 μg t.i.d. was selected for this study. On day 13 and 14, OGTT and gastric emptying were measured, and DSSS, SF-36, and a global assessment questionnaire were filled out by the patient. This was followed by a 1-week wash-out and the second treatment of 2 weeks with the same assessments on the last 2 days. The study was approved by the Leuven ethics committee in 2008 (S51131; ML5055). The study was registered as NCT01895296.

Data analysis

Early and late dumping severity scores were calculated by adding the severities of all early, respectively, late dumping symptoms. A cumulative dumping severity score was obtained by adding early and late scores.

The OGTT was considered positive when late HG occurred (glycemia <60 mg/dL at 150 or 180 min), when there was a rise in hematocrit of >10% over baseline value at 30 min, or when a PR increase of >10 bpm occurred at 30 min. The results of the $^{13}CO_2$ and $^{14}CO_2$ breath tests were analyzed as previously described.

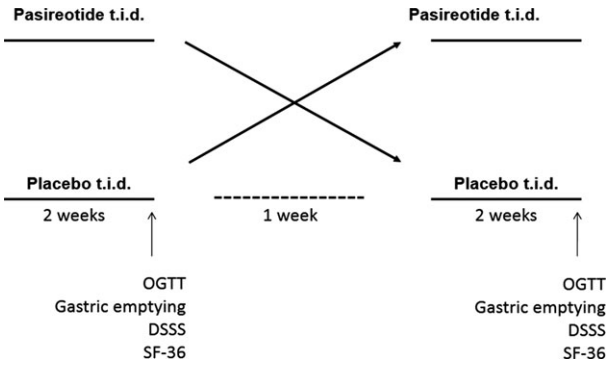

Figure 1 Schematic outline of the study. This was a double-blind *placebo*-controlled cross-over study with pasireotide or *placebo*, incorporating a number of mechanistic endpoints derived from oral glucose tolerance testing (OGTT) and gastric emptying testing. Dyspepsia symptom severity scores (DSSS) and quality of life (SF-36) were also assessed.

Statistical analysis

Results are expressed as means ± SEMs. Data were analyzed according to an intention-to-treat analysis. In case of early discontinuation or missing data, last observation carried forward (LOCF) method using baseline data was used, when these were available. For the symptom questionnaires, the questionnaire was filled out at the time of discontinuation. For the objective measurements (dumping provocation test), identical values to the pretreatment screening were assumed. A paired Student's *t*-test was used to compare results with both treatments. A $p < 0.05$ was considered significant.

RESULTS

Patients

Nine patients (six women, mean age 47 ± 4 years) with a clinical diagnosis of dumping syndrome after previous upper abdominal surgery (gastric bypass in three, partial gastrectomy in two, Nissen fundoplication in two, esophagectomy and total gastrectomy each in one) were enrolled in the study. All patients continued to experience dumping symptoms in spite of specific dietary measures.[1] In their history, six had documented HG during an oral glucose tolerance test, and one had a documented history of spontaneous HG. All had an abnormal OGTT at baseline (see below). Based on the baseline OGTT, objective signs of early dumping were present in six of the nine patients (PR or hematocrit rise), and objective signs of late dumping (HG) were present in seven of the nine patients. Based on the symptom questionnaire, all patients had symptoms of both early and late dumping (see below).

Conduct of the study

Five patients were randomized to *placebo* first and four to pasireotide first. During the first treatment phase, two patients dropped out because of adverse

gastrointestinal events. The adverse events included nausea, abdominal pain and cramps, and diarrhea. The onset of these adverse events was on the first day of administration, shortly after the first dose. The diarrhea aspect as described by the patient was most suggestive of steatorrhoea. Symptom scores for the second treatment phase, and OGTT data for both treatment phases were imputated by carrying the baseline observation forward. The other seven patients finished the double-blind *placebo*-controlled part of the study as planned.

Oral Glucose Tolerance Test

At baseline, the glucose challenge test was associated with a significant increase in glycemias at 30 and 60 min postingestion (from 87.2 ± 4.4 to respectively 149.9 ± 18.8 and 186.7 ± 29.4 g/dL, both $p < 0.01$) and a significant decrease at 180 min (61.0 ± 6.1 mg/dL, both $p < 0.01$; Fig. 2). Peak and nadir glycemias during the OGTT were 198.9 ± 27.3 and 58.7 ± 6.2 mg/dL, respectively. In addition, a significant rise in PR (from 69.8 ± 4.4 to respectively 82.0 ± 5.8 and 82.2 ± 4.0 bpm, both $p < 0.05$) occurred at 30 and 60 min (Fig. 3) and a small increase in hematocrit occurred at 30 min, which did not reach statistical significance. Insulin levels rose significantly from 8.8 ± 1.6 pmol/L at baseline to 118.3 ± 33.3 and 162.8 ± 52.7 at respectively 30 and 60 min ($p < 0.05$, Fig. 4). No significant changes in systolic or diastolic blood pressures occurred throughout the test (details not shown). The OGTT was pathological in all patients based on a rise in PR ($n = 5$), a rise in hematocrit ($n = 1$) or on late hypoglycemia ($n = 7$).

Due to drop out of two patients during the first treatment phase, glucose tolerance testing on therapy was available for only seven patients, but values were imputated from baseline using LOCF. Compared to baseline, 14 days treatment with *placebo* s.c. t.i.d. had no significant effect on any of the parameters studied. Compared to *placebo*, treatment with pasireotide s.c. suppressed the increase in PR (8.2 ± 3.5 *vs* 17.1 ± 2.8 bpm, $p = 0.02$) and the late hypoglycemia (nadir glycemias 55.6 ± 4.3 *vs* 83.3 ± 9.5 mg/dL, $p = 0.007$; Figs 2–4). During pasireotide treatment, compared to *placebo*, PR was significantly lower at 30, 60, and 120 min of the OGTT.

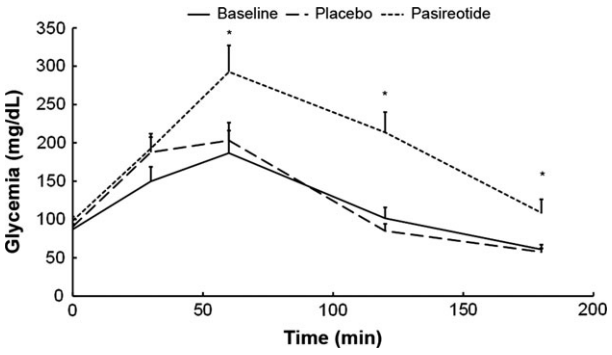

Figure 2 Mean glycemia levels during oral glucose tolerance testing at baseline and during treatment with pasireotide or *placebo* s.c.
*$p < 0.05$ compared to *placebo*.

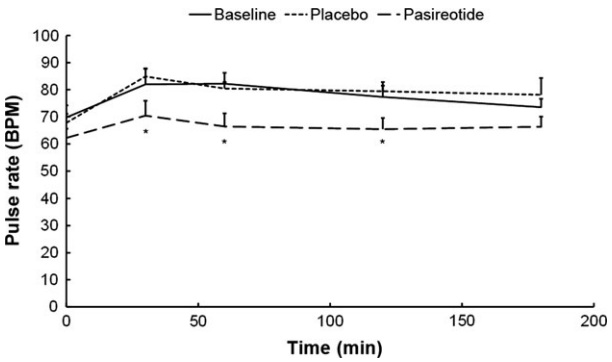

Figure 3 Mean pulse rate during oral glucose tolerance testing at baseline and during treatment with pasireotide or *placebo* s.c.
*$p < 0.05$ compared to *placebo*.

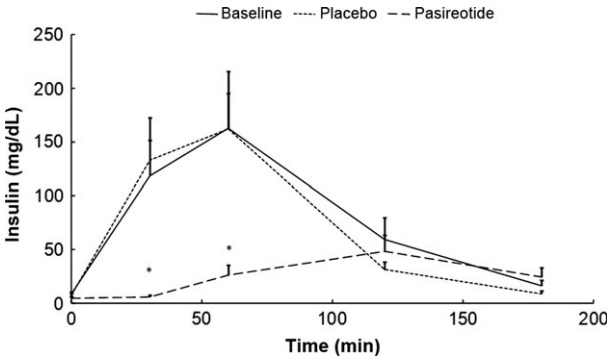

Figure 4 Mean insulin levels during oral glucose tolerance testing at baseline and during treatment with pasireotide or *placebo* s.c.
*$p < 0.05$ compared to *placebo*.

The peak glycemia was significantly higher after pasireotide s.c. compared to *placebo* (294.1 ± 33.3 *vs* 221.0 ± 23.2 mg/dL, $p = 0.002$). After 14 days of treatment with pasireotide s.c. 300 μg t.i.d., two of the seven per-protocol patients still had a pathological OGTT (based on PR in two) compared to six of seven on *placebo* (PR in six, hematrocrit in three and hypoglycemia in four).

Peptide hormone levels

Insulin levels were significantly lower after pasireotide at most time points during the oral glucose tolerance

test (Fig. 3). Compared to *placebo*, glucagon levels after pasireotide did not differ at 0 (188.3 ± 7.5 *vs* 195.8 ± 7.2 pg/dL, NS) and 30 min (171.4 ± 7.2 *vs* 210.7 ± 28.5 pg/dL, NS), but were significantly lower at 60, 120, and 180 min after the glucose load (respectively 166 ± 9.1 *vs* 201.1 ± 13.8 pg/dL, $p < 0.05$; 159 ± 8.1 *vs* 210 ± 13.5 pg/dL, $p < 0.05$; and 155.6 ± 3.8 *vs* 237.1 ± 16.5 pg/dL, $p < 0.005$). Fasting gastrin levels were also significantly lower after pasireotide treatment (39.7 ± 3.2 *vs* 48.1 ± 5.3 pg/dL, $p < 0.05$).

Gastric emptying breath test

Gastric emptying was performed in only seven patients after 2 weeks treatment with pasireotide or *placebo*. After pasireotide treatment, compared to *placebo*, significant delays in the simultaneously measured gastric emptying rates of solids (t1/2 83.0 ± 23.8 *vs* 42.9 ± 8.7 min, $p = 0.05$) and liquids (t1/2 70.0 ± 10.4 *vs* 40.2 ± 4.1 min, $p = 0.05$) were observed. Changes in solid or liquid emptying after pasireotide compared to *placebo* treatment were not significantly correlated with changes in OGTT values.

Dumping symptom score

Baseline severity scores for total, early, and late dumping symptoms are shown in Fig. 5. Symptom levels for both early and late dumping were high in all patients. No significant differences in symptom severity scores were observed with pasireotide or *placebo*.

Quality of life questionnaire

SF-36 scores are summarized in Table 1. No significant differences were observed with pasireotide or *placebo*.

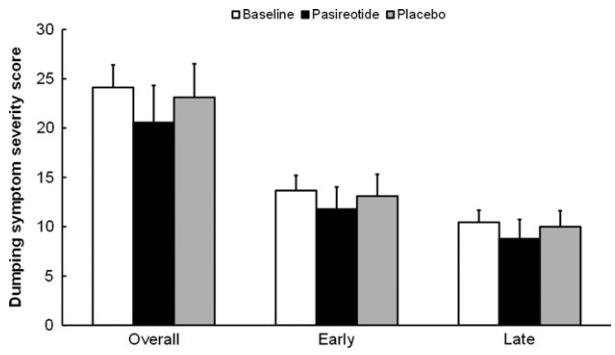

Figure 5 Total, early, and late dumping severity at baseline and during treatment with pasireotide or *placebo* s.c. Data are shown according to intention-to-treat analysis.

Adverse events

No serious adverse events occurred. Two patients interrupted the study during the first treatment phase because of gastrointestinal symptoms (abdominal cramps and pain, nausea, and diarrhea). Both had been randomized to pasireotide first. During *placebo* treatment, reported adverse events included diarrhea ($n = 2$), abdominal pain ($n = 1$), and a transient flu-like episode ($n = 1$). During treatment with pasireotide, the adverse event reporting included nausea ($n = 4$), diarrhea ($n = 6$), mild skin irritation at injection site ($n = 2$), abdominal pain ($n = 3$), and decreased appetite ($n = 1$).

The baseline ultrasound reported cholecystectomy in five patients and gallbladder microlithiasis in one patient. No biliary symptoms or complications occurred during the study.

DISCUSSION

The prevalence of postoperative dumping syndrome is increasing worldwide due to the increased application of bariatric surgery. Currently available treatment strategies include dietary measures, acarbose and SA and surgical interventions or continuous enteral feeding for refractory cases.[1] The short-acting SA octreotide is the best studied treatment option for postoperative dumping, but its application is not devoid of side effects and long-term use is problematic because of loss of patient compliance over time because of the three injections per day, and possibly also decreased symptom control over time.[1,8,12,13] Administration of long-acting release octreotide offers a more attractive alternative by reducing the three injections a day to 1 monthly injection with comparable efficacy, although patients with severe dumping syndrome prefer the short-acting formulation.[1,8,12,13] However, a subgroup of up to 60% of patients with dumping syndrome is insufficiently responding to currently available SA in the short or long term.[1,8,12,13]

Based on a higher affinity for a larger number of somatostatin receptors, pasireotide has the potential to provide a more potent treatment option for dumping syndrome.[14] Indeed, studies in intestinal cultures have shown that pasireotide has a superior inhibitory effect on the release of GLP-1 and PYY compared to octreotide.[15,16] In a phase 2 study, pasireotide was effective in patients with neuroendocrine tumors that did not respond to octreotide.[21]

In the present pilot study, we evaluated the effect of pasireotide on objective and subjective parameters in postoperative dumping syndrome. We observed that

treatment with pasireotide provided significant improvement of clinically relevant pathophysiological features of both early (PR) and late (HG) dumping. During the oral glucose tolerance test, insulin and glucagon levels were significantly lower after pasireotide treatment. Similar to octreotide, pasireotide also inhibited baseline gastrin levels.[22]

These biochemical actions of pasireotide were accompanied by a significant delay in gastric emptying, which may also contribute to improvement of dumping syndrome symptoms,[1] although changes in gastric emptying did not correlate significantly with biochemical changes measured during the OGTT. The value of the liquid half emptying time in our patient cohort may seem longer than one would expect in dumping syndrome. As the assessment of solid and liquid emptying occurred simultaneously, the presence of the solid meal has a slowing effect on liquid emptying too. However, the test is still susceptible to pharmacological influences, and with pasireotide a robust slowing of liquid (and solid) emptying was found. No significant improvement in DSSS or SF-36 was observed, but this may at least in part be attributable to the small sample size of the study.

The magnitude of the changes in gastric emptying rate and glycemia during the OGTT we observed in this study show a large effect size. Although no direct comparison occurred, the pharmacodynamics effects of pasireotide on these parameters seems superior to what has been observed with octreotide.[1,8,23] Hence, the observations support the potential for pasireotide to have a bigger therapeutic efficacy than octreotide, but this will need further addressing in future clinical trials.

No major adverse events occurred, but some side effects of pasireotide therapy were reported and two patients stopped treatment because of gastrointestinal adverse events, while being randomized to pasireotide. These side effects may also have contributed to the lack of significant improvement with pasireotide on the DSSS. Taking into account the magnitude of the effects of pasireotide on gastric emptying, glycemia's and peptide release, it seems conceivable that lower doses of pasireotide may also show efficacy on pathophysiological mechanisms underlying dumping syndrome, while potentially inducing less gastrointestinal side effects. Based on these considerations, an ongoing follow-up study uses a dose-escalation paradigm to define the optimal dosing of pasireotide in dumping syndrome.[24]

The current study has a number of limitations. First of all, the number of subjects studied is small, and only one dose of pasireotide was evaluated, but this is in keeping with the mechanistic proof-of-concept nature of the study. Secondly, the gastric emptying test evaluated liquid and solid emptying at the same time, which slowed the measured rates of liquid emptying. Thirdly, the OGTT used relatively long intervals (60 min) for the measurements; shorter intervals might have increased the sensitivity for demonstrating pasireotide effects. Furthermore, some studies have assessed dumping syndrome symptoms during the OGTT. In this study, we only used a recall questionnaire to assess symptom severity. This has the advantage of assessing symptom burden as it occurs in real life, but it is conceivable that the measurement during the standardized circumstance of the OGTT has higher sensitivity for changes in symptoms, and this should be addressed in future studies.

In summary, we demonstrated in this pilot study that treatment with pasireotide 300 μg s.c. t.i.d. affects pathophysiological features underlying both early and late dumping syndrome symptoms, and was devoid of major adverse events. These observations provide a rationale for larger scale evaluation of its therapeutic potential in dumping syndrome patients. Future studies should also explore lower doses of pasireotide and longer treatment periods.

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DISCLOSURE

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