This search summary contains the results of a literature search undertaken by the
Lincolnshire Knowledge and Resource Service librarians in;
August 2014

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If you would like this search re-run with a different focus, or updated to accommodate papers published since the search was completed, please let us know. This literature searching service is available to support public health / health and social care commissioning in Lincolnshire.

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Disclaimer
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“Google can bring you back 100,000 answers, a librarian can bring you back the right one.”
Neil Gaiman
“Google can bring you back 100,000 answers, a librarian can bring you back the right one.”

Neil Gaiman
Individual Funding Request Literature Search Results

**Search request date:** 31st August 2014  
**Search completion date:** 1st September 2014  
**Search completed by:** Jan Badcock

**IFR Request**

IFR 7598; Octreotide/Lanreotide for dumping syndrome and faecal incontinence and the incidence/prevalence of 'post-vagotomy' faecal incontinence. I've attached the paper provided by the referrer.

Papers already found:  
Therapeutic value of octreotide for patients with severe dumping syndrome- A review of randomised control trials.

Octreotide therapy in dumping syndrome: analysis of long term results.

Outcome of Search  
No new systematic reviews, RCTS found on the use of Octreotide for dumping syndrome.

No systematic reviews, RCTS found on the use of Lanreotide for faecal incontinence.

No connection found between faecal incontinence and vageotomy, although it is known to cause diarrhoea and steatorrhea.

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Dumping Syndrome - Medscape

Anatomic structures of the stomach are divided into the cardia, fundus, body, and pylorus. The fundus serves as the reservoir for ingested meals, while the distal stomach churns and mixes with digestive enzymes and initiates the digestive process. Once the foods are processed, the pylorus releases the food in a controlled fashion downstream into the duodenum.

The capacity of the stomach in adults is approximately 1.5-2 liters, and its location in the abdomen allows for considerable distensibility. Gastric motility is controlled by myogenic (intrinsic), circulating hormonal, and neural activity (gastric plexus, myenteric plexus, sympathetic and parasympathetic nerves). Alterations in gastric anatomy after surgery or interference in its extrinsic innervation (vagotomy) may have profound effects on the gastric reservoir and pyloric sphincter mechanism and, in turn, affects gastric emptying. These effects, for convenience, have been termed postgastrectomy syndromes.

Postgastrectomy syndromes include small capacity, dumping syndrome, bile gastritis, afferent loop syndrome, efferent loop syndrome, anemia, and metabolic bone disease. Postgastrectomy syndromes are iatrogenic conditions that may arise from partial gastrectomies, independent of whether the gastric surgery was initially performed for peptic ulcer disease, cancer, or weight loss (bariatric). The surgical procedures include Billroth-I, Billroth-II, and Roux-en-Y.\[Ref1\]

_Hertz made the association between postprandial symptoms and gastroenterostomy in 1913._[1]_ Hertz stated that the condition was due to "too rapid drainage of the stomach." Wyllys et al first used the term "dumping" in 1922 after observing radiographically the presence of rapid gastric emptying in patients with vasomotor and GI symptoms._[2]_

**Pathophysiology**

Dumping syndrome is the effect of altered gastric reservoir function, abnormal postoperative gastric motor function, and/or pyloric emptying mechanism.\[Ref2\] See the image below.
Pathophysiology of dumping syndrome.
Clinically significant dumping syndrome occurs in approximately 10% of patients after any type of gastric surgery and in up to 50% of patients after laparoscopic roux-en-Y gastric bypass. Dumping syndrome has characteristic alimentary and systemic manifestations. It is a frequent complication observed after a variety of gastric surgical procedures, such as vagotomy, pyloroplasty, gastrojejunostomy, and laparoscopic Nissan fundoplication. Dumping syndrome can be separated into early and late forms, depending on the occurrence of symptoms in relation to the time elapsed after a meal.

Postprandially, the function of the body of the stomach is to store food and to allow the initial chemical digestion by acid and proteases before transferring food to the gastric antrum. In the antrum, high-amplitude contractions triturate the solids, reducing the particle size to 1-2 mm. Once solids have been reduced to this desired size, they are able to pass through the pylorus. An intact pylorus prevents the passage of larger particles into the duodenum. Gastric emptying is controlled by fundic tone, antropyloric mechanisms, and duodenal feedback. Gastric surgery alters each of these mechanisms in several ways.

Gastric resection reduces the fundic reservoir, thereby reducing the stomach's receptiveness (accommodation) to a meal. Vagotomy increases gastric tone, similarly limiting accommodation. An operation in which the pylorus is removed, bypassed, or destroyed increases the rate of gastric emptying. Duodenal feedback inhibition of gastric emptying is lost after a bypass procedure, such as gastrojejunostomy. Accelerated gastric emptying of liquids is a characteristic feature and a critical step in the pathogenesis of dumping syndrome. Gastric mucosal function is altered by surgery, and acid and enzymatic secretions are decreased. Also, hormonal secretions that sustain the gastric phase of digestion are affected adversely. All these factors interplay in the pathophysiology of dumping syndrome.

The accommodation response and the phasic contractility of the stomach in response to distention are abolished after vagotomy or partial gastric resection. Early dumping syndrome and reflux gastritis are less frequent when segmented gastrectomy rather than distal gastrectomy is performed for early gastric cancer. In persons with long segment Barrett esophagus treated with a truncal vagotomy, partial gastrectomy, and roux-en-Y gastrojejunostomy, 41% developed dumping within the first 6 months after surgery, but severe dumping is rare (5% of cases).
The dumping syndrome occurs in 45% of persons who are malnourished and who have had a partial or complete gastrectomy.\textsuperscript{[6]}

The late dumping syndrome is suspected in the person who has symptoms of hypoglycemia in the setting of previous gastric surgery, and this late dumping can be proven with an oral glucose tolerance test (hyperinsulinemic hypoglycemia), as well as gastric emptying scintigraphy, which shows the abnormal pattern of initially delayed and then accelerated gastric emptying.\textsuperscript{[7]}

http://emedicine.medscape.com/article/173594-overview#a0101

**Incidence and Prevalence**

No information could be found in the connection between faecal incontinence and vagotomy.  
Sources checked: NHS Evidence, Medline, EMBASE, Cinahl, NICE, Cochrane TRIP database, NHS Choices, Medscape, google custom.

**Drug Name**

NHS Evidence - Medicines

**BNF**

**OCTREOTIDE**

[**Additional information** interactions (Octreotide)].

**Indications**

see under Dose

**Cautions**

see Cautions (somatostatin analogues); monitor thyroid function on long-term therapy; monitor liver function; interactions: Appendix 1 (octreotide)

**Hepatic impairment**

adjustment of maintenance dose of non-depot preparations may be necessary in patients with liver cirrhosis

**Pregnancy**

possible effect on fetal growth; manufacturer advises use only if potential benefit outweighs risk and effective contraception required during treatment

**Breast-feeding**

manufacturer advises avoid—present in milk in *animal* studies
**Side-effects**
see Somatostatin analogues (Malignant disease and immunosuppression); also arrhythmias, bradycardia, dyspnoea, headache, dizziness, dehydration, alopecia, rash; hepatitis also reported

**Dose**
- Symptoms associated with carcinoid tumours with features of carcinoid syndrome, VIPomas, glucagonomas, by subcutaneous injection, initially 50 micrograms once or twice daily, gradually increased according to response to 200 micrograms 3 times daily (higher doses required exceptionally); maintenance doses variable; in carcinoid tumours discontinue after 1 week if no effect; if rapid response required, initial dose by intravenous injection (with ECG monitoring and after dilution to a concentration of 10–50% with sodium chloride 0.9% injection)
- Acromegaly, short-term treatment before pituitary surgery or long-term treatment in those inadequately controlled by other treatment or until radiotherapy becomes fully effective by subcutaneous injection, 100–200 micrograms 3 times daily; discontinue if no improvement within 3 months
- Prevention of complications following pancreatic surgery, consult product literature

https://www.evidence.nhs.uk/about-evidence-services/content-and-sources/medicines-information

**LANREOTIDE**

**Additional information** interactions (Lanreotide).

**Indications**
see notes above

**Cautions**
see Somatostatin analogues (Malignant disease and immunosuppression); cardiac disorders (including bradycardia); interactions: Appendix 1 (lanreotide)

**Pregnancy**
manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding**
manufacturer advises caution—no information available

**Side-effects**
see Somatostatin analogues (Malignant disease and immunosuppression); also reported constipation, dyspepsia, bradycardia, asthenia, dizziness, fatigue, raised bilirubin, biliary dilatation, alopecia; less commonly skin nodule, hot flushes, leg pain, malaise, headache, insomnia, tenesmus, decreased libido, drowsiness, pruritus, increased sweating; rarely hypothyroidism (monitor as necessary)

License Indications

MHRA
None found for the use of Octreotide/Lanreotide for dumping syndrome or faecal incontinence

FDA Drug Approvals
None found for the use of Octreotide/Lanreotide for dumping syndrome or faecal incontinence

Evidence

Sources checked: NHS Evidence, Medline, EMBASE, Cinahl, NICE, Cochrane TRIP database, NHS Choices, Medscape, google custom

Guidelines

Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer

Dumping syndrome
When gastric emptying is rapid it leads to ‘dumping syndrome’, characterised by GI and vasomotor symptoms that occur after meals. This can be soon after meals or delayed for up to several hours. The physiological causes are complex, but include the high osmolarity of small bowel contents and reactive hypoglycaemia. The diagnosis of early dumping is usually made on clinical grounds, although rarely gastric scintigraphy is helpful. Late dumping can be diagnosed by measuring blood glucose when patients are symptomatic. If the presentation is atypical, the rare possibility of an insulinoma should be considered. Initial management should be dietary advice to reduce the volume and osmolarity of food presented to the small intestine and the avoidance of fluids taken with meals. Loperamide, guar gum or pectin to slow gastric emptying may be helpful. For late dumping, acarbose may sometimes help. Octreotide or lanreotide are helpful in the short term. Studies have shown mixed results when these drugs were evaluated longer term. Surgical revision of the roux-en-Yanastomosis is a complex procedure but can be effective in selected cases.


Systematic Reviews & Meta Analyses
None found
Sources checked: NHS Evidence, Medline, EMBASE, Cinahl, NICE, Cochrane TRIP database, NHS Choices, Medscape, google custom

Cochrane
None Found
Sources checked: NHS Evidence, Medline, EMBASE, Cinahl, NICE, Cochrane TRIP database, NHS Choices, Medscape, google custom

Literature Reviews
None found
Sources checked: NHS Evidence, Medline, EMBASE, Cinahl, NICE, Cochrane TRIP database, NHS Choices, Medscape, google custom
Efficacy of the long-acting repeatable formulation of the somatostatin analogue octreotide in postoperative dumping.

Citation: Clinical Gastroenterology & Hepatology, April 2009, vol./is. 7/4(432-7), 1542-3565;1542-7714 (2009 Apr)

Author(s): Arts J; Caenepeel P; Bisschops R; Dewulf D; Holvoet L; Piessevaux H; Bourgeois S; Sifrim D; Janssens J; Tack J

Abstract: BACKGROUND & AIMS: Several studies have established symptomatic and mechanistic benefits of the somatostatin analogue octreotide in patients with dumping syndrome, but clinical use is hampered by the requirement for subcutaneous administration 3 times daily. We compared the efficacy of subcutaneous octreotide with that of the long-acting repeatable (LAR) octreotide formulation, which is administered monthly, in patients with dumping syndrome

METHODS: The study included 30 consecutive patients with postoperative dumping, evidenced by oral glucose tolerance test (OGTT) results and insufficient response to dietary measures. OGTT, dumping severity score (summary of scores 0-3 for 8 early and 6 late dumping symptoms), and quality-of-life data were evaluated at baseline, after 3 days of subcutaneous administration of octreotide (0.5 mg), and then after 3 monthly intramuscular injections of octreotide LAR (20 mg).

RESULTS: Both formulations of octreotide significantly reduced total dumping severity scores (21.7 +/- 1.6 at baseline, 11.2 +/- 1.2 for subcutaneous and 14.0 +/- 1.8 for LAR formulations; P < .05). This reduction was associated with significant improvements in the increase in pulse rate (13.8 +/- 5.8 at baseline vs -0.3 +/- 2.2 and 1.9 +/- 1.7; P < .05) as well as the increase in hematocrit level (4.0 +/- 1.4 at baseline vs 0.3 +/- 0.9 and 0.4 +/- 1.0; P < .05), and the lowest glycemia level in the OGTT (54.1 +/- 6.7 at baseline vs 98.9 +/- 7.1 and 67.8 +/- 5.9; P < .05). LAR octreotide administration significantly improved patients’ quality of life. Patients’ evaluations of their overall treatment efficacy was higher on LAR compared with the subcutaneous formulation (83% vs 52%; P = .01).

CONCLUSIONS: Monthly administration of LAR octreotide improves OGTT results, symptoms, and quality of life in patients with postoperative dumping.

Publication Type: Clinical Trial; Comparative Study; Journal Article; Multicenter Study; Research Support, Non-U.S. Gov't

Source: MEDLINE
Efficacy of depot long-acting release octreotide therapy in severe dumping syndrome
C. Penning, J. Vecht and A. A. M. Masclee
Alimentary Pharmacology & Therapeutics
Volume 22, Issue 10, November 2005

Introduction

Dumping syndrome occurs in 10% of all patients undergoing gastric surgery.\(^1\) The clinical picture consists of two subtypes, namely early and late dumping, which may be present together or separately. Early dumping is the result of rapid nutrient delivery into the small intestine and is characterized by abdominal symptoms such as diarrhoea, nausea, fullness and abdominal cramps. In addition, systemic vascular changes result in palpitations, headache and the wish to lie down. Late dumping occurs 1–3 h postprandially and is merely the result of reactive hypoglycaemia. Symptoms of late dumping are perspiration, dizziness and hunger.\(^1\)

Treatment of dumping syndrome depends on the severity of symptoms. In patients with mild symptoms, dietary adjustment usually is sufficient. In more severe cases, additional treatment with acarbose\(^2\) or dietary fibres\(^3\) might be necessary. However, in a small number of patients symptoms are refractory and daily subcutaneous (s.c.) injections with octreotide (OCT) are required.\(^3, 4\) Octreotide is a synthetic analogue of the brain–gut peptide somatostatin. It delays gastrointestinal transit\(^5, 6\) and has an inhibitory effect on insulin secretion\(^3\) and postprandial vasodilatation.\(^7\) Several studies have demonstrated the efficacy of daily injections of OCT in preventing symptoms of early and late dumping.\(^8, 9\) However, side-effects such as steatorrhea, nausea and painful injection sites occur frequently.\(^8–10\) We have previously shown that despite initial efficacy, many patients discontinue using OCT because of side-effects and the need for repeated daily s.c. injections.\(^10\)

Depot long-acting release OCT (Sandostatin-LAR, LAR) might be considered in these patients. Monthly instead of daily injections may improve overall well being and reduce side-effects related to repeated injections. Monthly LAR injections are a successful substitute for daily OCT injections in patients with acromegaly,\(^11, 12\) short bowel syndrome\(^13\) and patients with gastrointestinal neuro-endocrine tumours.\(^14, 15\) However, the efficacy of LAR in patients with dumping syndrome has not been evaluated. Our aim was to investigate the effect of LAR in a small cohort of patients with dumping syndrome and to compare results with those of s.c. OCT therapy. Emphasis was put on symptoms, quality of life (QOL) and side-effects. In addition, the study was dose finding to determine the optimal dose of LAR.
Materials and methods

Patients

Patients were recruited from the gastroenterology out-patient clinics of the Leiden University Medical Center and the Isala Medical Center in Zwolle. Twelve patients (five females, seven males) with severe dumping syndrome, previously proven by a dumping provocation test and not sufficiently responding to dietary measures or medication (apart from OCT), participated in this open study. Mean age was 58 ± 3 (mean ± S.E.M.) years. In all patients, dumping symptoms had started after a gastric surgical procedure and mean reported postsurgical weight loss was 13.0 ± 6.1 kg. Mean duration of symptoms was 10 ± 2 years. All patients had meal-related symptoms that occurred on a daily base that required daily use of OCT s.c. in order to control or prevent dumping symptoms. In two patients, OCT was administered continuously using a s.c. pump. Mean cumulative daily dose of OCT was 103 ± 41 μg (range: 50–150). None of the patients had cardiovascular or gastrointestinal disorders apart from dumping syndrome and none of them used concomitant cardiovascular medication. All patients gave informed consent. The study protocol has been approved by the local human medical ethics committee.

Study protocol

In this open study, patients were studied on six separate occasions during a period of 7 months. The first study visit occurred during their individual regimen of daily s.c. OCT injections (day −14). Directly after this visit, patients stopped using OCT. The second visit took place after a washout period of 14 day (day 0, washout). After the recordings on day 0, the first intragluteal injection of LAR (Novartis Pharma BV, Arnhem, the Netherlands) was administered. Patients were instructed to additionally apply their usual regimen of s.c. OCT injections during the first week after the initial LAR injection. The subsequent study visits were 14, 28, 90 and 180 days after the first LAR injection (visit LAR-1 to LAR-4). During visit LAR-1, patients did not visit the hospital but recorded their symptoms at home. The starting dose of LAR was 10 mg, but if necessary the dose could be increased to 20 mg, depending on the patient's symptomatic response to LAR 10 mg. Patients were allowed to discontinue LAR therapy because of lack of effect, side-effects, etc. The study design is shown in Table 1.
Table 1. Course of the study

<table>
<thead>
<tr>
<th>Visit</th>
<th>OCT (day −14)</th>
<th>Washout (day 0)</th>
<th>LAR-1 (day 14)</th>
<th>LAR-2 (day 28)</th>
<th>LAR-3 (day 90)</th>
<th>LAR-4 (day 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>2.</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

1. OCT, during daily s.c. octreotide injections; LAR-1 to LAR-4, visits during monthly Sandostatin-LAR injections; GIQLI, Gastrointestinal Quality of Life scale; s.c., subcutaneous.

2. Sandostatin-LAR injections were administered every month and on day 0, 28 and 180 directly after the recordings.

Dumping provocation test

Quality of life (GIQLI)  
Symptoms (diary)  
Food intake  
Faecal fat excretion  
Body weight

Dumping provocation test

In order to correlate the efficacy of LAR treatment to the severity of the untreated dumping symptoms, a dumping provocation test was performed during washout visit according to a previously described protocol. In brief, during this 4-h test under fasting conditions, symptoms were triggered by an oral load of 50 g glucose dissolved in 400 mL water. At regular time intervals, blood samples were obtained to determine blood glucose concentrations, and breath hydrogen ($H_2$) excretion and heart rate were monitored. The time to breath $H_2$ increase was defined as the time period (min) required for a breath $H_2$ increase of at least 10 p.p.m. over basal values. In addition, the maximal increase in heart rate (beats/min) over basal and the nadir blood glucose concentration (g/L) were calculated.
Quality of life

To evaluate the influence of therapy on QOL, the validated Gastrointestinal Quality of Life Index (GIQLI) questionnaire was used. This questionnaire consists of 36 questions, each of which with a maximum score of 4-points. The questionnaire addresses physical, emotional and social functioning, as well as gastrointestinal core symptoms and disease-specific symptoms. QOL was evaluated during OCT, washout and at LAR-2, LAR-3 and LAR-4.

Dumping symptoms

Presence and severity of dumping symptoms were evaluated using a symptom diary on a daily basis (for 1 week) before each study visit. The recorded symptoms were subdivided into abdominal symptoms (number of stools per day, stool consistency, abdominal pain, flatulence, abdominal cramps and bloating) and systemic symptoms (postprandial dizziness, postprandial palpitations, wish to lie down after meals, postprandial sweating or flushing and postprandial hunger feeling). The severity of each symptom was scored on a 10-points scale, the absence of a symptom was scored as 0. The systemic symptom score was defined by the total score of the separate systemic symptoms (range: 0–50), while the abdominal symptom score is the sum of the scores for abdominal pain, flatulence, abdominal cramps and bloating (range: 0–40). The composite symptom score is the sum of the systemic and the abdominal symptom score (range: 0–90).

Faecal fat excretion

Stools were collected for 24 h preceding day −14 (OCT), washout and LAR-2 and LAR-4. Total faecal weight was determined and fat content was measured according to a previously described method. Faecal fat excretion (%) was also calculated as the ratio of fat content (g) to stool weight (g).

Food intake

On the 2 consecutive days preceding the visits OCT, washout and LAR-2, patients recorded their intake of foods and drinks using a structured diary. The completed diaries were evaluated using the data on caloric contents of food (NEVO Table 1996).
**Body weight** Alterations in body weight were determined during OCT, washout and at days 28, 90 and 180. Weight gain was defined as the difference between body weight at day 180 during LAR treatment and body weight during OCT treatment.

**Analysis** Patients were subdivided into subgroups according to the dose of LAR they used at the end of the 6-month follow-up. The influence of LAR on body weight, dumping symptoms, QOL, food intake, dumping provocation test parameters and faecal fat excretion was analysed for all patients together and for the subgroups using the non-parametric Mann–Whitney rank sum test or, where appropriate, by ANOVA with Bonferroni's correction for multiple comparisons. Statistical comparisons between subgroups of patients were made using the non-parametric Mann–Whitney rank sum test or, where appropriate, Student's t-test for unpaired data. Results are expressed as mean ± S.E.M. The level of significance was set at $P < 0.05$.

**Results** None of the patients discontinued the use of LAR during the study. All patients started with a dose of 10 mg. However, during the follow-up, seven of 12 patients (58%) required a higher dose of 20 mg LAR, because of persistence of dumping symptoms. Mean age (53 ± 5 vs. 62 ± 4 years) and duration of symptoms (12 ± 3 vs. 8 ± 2 years) were not significantly different between patients who responded to 10 mg and patients requiring 20 mg. In addition, mean weight loss after surgery (12.7 ± 4.6 vs. 13.3 ± 7.7 kg) and mean daily cumulative dose of OCT (125 ± 43 vs. 88 ± 35 μg) were also comparable between patients responding with 10 and 20 mg.

At the end of the study, all patients were satisfied with LAR treatment. No serious adverse events had been observed. The intragluteal LAR injections were not painful. Reported abdominal and systemic side-effects of LAR treatment were similar to those of s.c. OCT.

**Quality of life**
During LAR treatment, GIQLI scores at all visits were significantly ($P < 0.01$) higher compared with washout and OCT (Table 2). Concerning its subscales, only the scale for ‘gastrointestinal core symptoms’ improved, and was significantly ($P < 0.01$) higher during LAR treatment compared with washout and OCT at all visits (Table 2).

| Table 2. Results of the effect measurements in all patients ($n = 12$) |
|----------------------|----------------|----------------|----------------|----------------|----------------|
| OCT (day −14)        | Washout (day 0)| LAR-1 (day 14)| LAR-2 (day 28) | LAR-3 (day 90) | LAR-4 (day 180)|
| 1. OCT, during daily s.c. octreotide injections; LAR-1 to LAR-4, visits during monthly Sandostatin-LAR injections; GIQLI, Gastrointestinal Quality of Life scale; s.c., subcutaneous. |
Table 2. Results of the effect measurements in all patients ($n = 12$)

<table>
<thead>
<tr>
<th></th>
<th>OCT (day −14)</th>
<th>Washout (day 0)</th>
<th>LAR-1 (day 14)</th>
<th>LAR-2 (day 28)</th>
<th>LAR-3 (day 90)</th>
<th>LAR-4 (day 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIQLI – overall score</td>
<td>74 ± 4</td>
<td>75 ± 6</td>
<td>92 ± 5*</td>
<td>87 ± 6*</td>
<td>88 ± 4*</td>
<td></td>
</tr>
<tr>
<td>GIQLI – core symptoms</td>
<td>43 ± 3</td>
<td>44 ± 4</td>
<td>52 ± 3*</td>
<td>53 ± 4*</td>
<td>52 ± 2*</td>
<td></td>
</tr>
<tr>
<td>Diary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite score</td>
<td>33 ± 6</td>
<td>35 ± 6</td>
<td>30 ± 5</td>
<td>31 ± 5</td>
<td>27 ± 6</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>18 ± 3</td>
<td>19 ± 3</td>
<td>16 ± 3</td>
<td>17 ± 3</td>
<td>13 ± 3</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>15 ± 3</td>
<td>15 ± 4</td>
<td>13 ± 3</td>
<td>15 ± 3</td>
<td>14 ± 3</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>Food intake (kcal)</td>
<td>1539 ± 265</td>
<td>1361 ± 227</td>
<td>1609 ± 235</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faecal fat output (g/24 h)</td>
<td>38 ± 9</td>
<td>12 ± 4†</td>
<td>19 ± 5†</td>
<td>28 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faecal fat excretion (m%)</td>
<td>9 ± 2</td>
<td>6 ± 2</td>
<td>9 ± 1</td>
<td>10 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>67 ± 4</td>
<td>66 ± 4</td>
<td>68 ± 4</td>
<td>69 ± 3</td>
<td>70 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

2. * $P < 0.05$ vs. OCT and washout; † $P < 0.05$ vs. OCT.

Dumping symptoms (diary)

Mean composite symptom scores and mean abdominal and systemic symptom scores are listed in Table 2. During LAR treatment, the composite symptom score decreased, although not significantly, from 33 ± 6 (OCT) to 28 ± 5 (LAR–4). Compared with OCT and washout, neither abdominal nor systemic symptom scores decreased significantly during LAR treatment.
Food intake

Mean daily caloric and fat intake are listed in Table 2. During the study, no significant alterations in caloric intake were observed.

Fecal fat excretion

During OCT, 24 h faecal fat output was significantly ($P = 0.02$) higher compared with washout (Table 2). During LAR treatment, fat output gradually increased: fat output was significantly ($P < 0.05$) reduced at visit LAR-2 compared with OCT, but at visit LAR-4 there was no significant difference with OCT. Faecal fat excretion ratio however, was not different between OCT, washout and LAR treatment.

Body weight

During washout, body weight was lower compared with OCT in all patients (Table 2). During LAR treatment, a non-significant increase in body weight was observed ($P = 0.19$).

Dumping provocation test

A provocation test was performed during washout. Results are listed in Table 3. When comparing the initial test results of patients responding to 10 mg with those requiring 20 mg, only the time to breath H$_2$ increase was significantly ($P < 0.05$) shorter in the patients with an end dose of 10 mg.

<table>
<thead>
<tr>
<th></th>
<th>All patients ($n = 12$)</th>
<th>End dose 10 mg ($n = 5$)</th>
<th>End dose 20 mg ($n = 7$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Time to breath H$_2$ increase (min)</td>
<td>34 ± 6</td>
<td>21 ± 6*</td>
<td>43 ± 6</td>
</tr>
<tr>
<td>2. Maximum increase in heart rate (bpm) in first hour</td>
<td>13 ± 1</td>
<td>13 ± 2</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>3. Nadir blood glucose concentration (g/L)</td>
<td>3.2 ± 0.2</td>
<td>3.3 ± 0.2</td>
<td>3.1 ± 0.2</td>
</tr>
</tbody>
</table>

1. bpm, beats per minute.

2. * $P < 0.05$ vs. end dose 20 mg.
Patients with end dose 10 vs. 20 mg

When comparing the results between patients responding to 10 mg and those requiring 20 mg, we observed a number of differences in the efficacy of LAR. Overall GIQLI scores for both subgroups of patients are illustrated in Figure 1. A significant ($P < 0.05$) increase of the overall GIQLI score during LAR treatment was observed only in patients with end dose 10 mg. The composite symptom score decreased only in patients with an end dose 10 mg of LAR. This difference was significant ($P = 0.02$) at visit LAR-3 (Figure 2a).

Figure 1. Mean Gastrointestinal Quality of Life Index (GIQLI) scores in five patients with an end dose of 10 mg Sandostatin-LAR (open bars) and in seven patients with an end dose of 20 mg Sandostatin-LAR (grey bars) during subcutaneous (s.c.) octreotide injections (OCT), washout, after 28 (LAR-2), 90 (LAR-3) and 180 (LAR-4) days of Sandostatin-LAR treatment. * $P < 0.05$, between groups.

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Figure 2. Mean composite symptom scores (a) and mean abdominal symptom scores (b) from the diary in five patients with an end dose of 10 mg Sandostatin-LAR (open bars) and in seven patients with an end dose of 20 mg Sandostatin-LAR (grey bars) during subcutaneous (s.c.)
octreotide injections (OCT), washout, after 14 (LAR-1), 28 (LAR-2), 90 (LAR-3) and 180 (LAR-4) days of Sandostatin-LAR treatment. * \( P < 0.05 \), between groups.

During LAR treatment, the abdominal symptom score decreased in the patients with end dose 10 mg (Figure 2b). This difference was significant (\( P < 0.05 \)) at visits LAR-1, LAR-2 and LAR-3 compared with patients requiring 20 mg. In addition, the mean systemic symptom score was significantly (\( P < 0.001 \)) reduced in patients with end dose 10 (6 ± 2) compared with end dose 20 mg (18 ± 5; data not shown) at visit LAR-3.

Body weight increased but the increase was not statistically significant. Overall weight gain in patients with end dose 10 mg (4.2 ± 1.6 kg) was higher (\( P = 0.18 \)) than in patients with end dose 20 mg (1.5 ± 1.8 kg).

**Discussion**

Treatment with monthly LAR injections offers an adequate alternative for daily OCT injections in patients requiring continuous treatment with a somatostatin analogue. This has been demonstrated previously in patients with acromegaly, short bowel syndrome and patients with gastrointestinal neuro-endocrine tumours. This is the first study to report on the efficacy of depot OCT in patients with severe dumping syndrome.

Apart from previously reported side-effects such as painful injection sites, the necessity of self-administered daily s.c. injections may also have social implications for the patient. A recent study in diabetic patients comparing QOL during multiple daily injections and continuous infusion, demonstrated that switching to continuous infusion resulted in a significant increase in daily and social activities. In the present study, we observed that LAR treatment caused a significant increase in QOL. However, only the score on the gastrointestinal symptoms subscale increased significantly, but not the scores on the subscales of social, emotional and physical functioning. Our interpretation is that the efficacy of depot OCT treatment compared with s.c. OCT cannot be assigned only to an improvement in overall well being, but that depot OCT is also more effective in suppressing gastrointestinal symptoms than s.c. OCT injections. This is also reflected by a reduction in the symptom scores from the diary during LAR treatment. Although we observed significant improvement of the GIQLI core symptoms subscale during LAR treatment, the increase of the abdominal symptom score obtained by diary was not significant.
We believe that this discrepancy is due to different sensitivity of both instruments: the GIQLI covers multiple abdominal symptoms \((n = 19)\) with scores from 0 to 4, scoring in retrospect, whereas abdominal symptom score from diary includes only four symptoms with a wider range (0–10) and scoring every day for 7 days. As a result, the first is more likely to represent an overall impression.

Recorded symptom scores during washout were lower than might be expected in these patients with severe, invalidating dumping symptoms. In our opinion, this results from coping strategies (for instance: food avoidance) that the patients had developed post-operatively. This might have affected symptom scores. To date, patients lost 1 kg of weight in the 14-day washout period.

Patients with dumping syndrome are typically underweight, because of malabsorption or malassimilation and reduced caloric intake. Ghrelin is involved in eating behaviour and satiety. As treatment with somatostatin analogues suppresses plasma ghrelin levels\(^{20,21}\) and thereby appetite, weight loss might continue during treatment. During LAR treatment however, we observed an increase in body weight. Caloric intake increased during depot OCT although not significantly. In addition, faecal fat excretion during depot OCT (visit LAR-2) was significantly lower compared with OCT s.c. The observed increase in body weight may have contributed to the increase of QOL during LAR treatment.

When analysing the results of patients responding to a dose of 10 mg and those requiring 20 mg, it became clear that the patients on 10 mg LAR improved most. In these patients we observed a significant improvement in QOL, a significant decrease of abdominal symptoms and an increase in body weight. No improvement was observed in patients requiring a dose of 20 mg. It is of interest to know whether responders can be identified from non-responders based on clinical characteristics or on the results of the initial dumping provocation test. Age, gender, type of surgery and duration of dumping symptoms were not different between the subgroups. However, during the dumping provocation test performed during washout, the time to breath \(H_2\) increase was significantly shorter in patients with an end dose of 10 mg LAR, implying that proximal gastrointestinal transit in these patients is more accelerated. As OCT significantly delays proximal gastrointestinal transit,\(^{5,6}\) this finding could account for the more pronounced reduction of abdominal symptoms during LAR treatment in patients with an end dose of 10 mg. The gain in weight in these patients might result from more efficient absorption of nutrients because of prolonged contact between nutrients and the intestinal mucosa.
When patients felt they did not sufficiently respond to 10 mg LAR at or after the visit on day 28, dose adjustment to 20 mg was allowed. But the patients requiring 20 mg remained to show less clinical improvement. The reason for the lower efficacy of even a higher OCT dose is not apparent. Apart from the above-mentioned factor of intestinal transit, differences in somatostatin receptor subtypes or receptor density may be involved.

We are well aware that the design of our study has limitations. First, the study was not placebo-controlled and secondly, based on subjective criteria (patient's impression) the dose of LAR was increased. Nowadays, dumping syndrome is rare because gastric surgery is no longer performed to treat peptic ulcer disease. Even in specialized referral centres only a small number of patients is treated with OCT for dumping syndrome.

A larger randomized-controlled clinical trial is therefore not feasible. Because of symptom severity and the availability of effective therapy (OCT s.c.), a placebo-controlled study of depot OCT was considered unethical. In addition, we realize that the results might have been influenced by the increased follow-up frequency during the study, in comparison with patients’ usual 3-monthly visits. However, the interval between the last study visits was 90 days, while clinical parameters during the last study visit were still significantly improved. Therefore, we think that the positive effect of increased follow-up is minimal in the present study.

In conclusion, we have demonstrated that LAR is at least as effective as OCT s.c. in suppressing symptoms in patients with severe dumping syndrome and is more effective than OCT s.c. in increasing body weight and QOL. In patients not sufficiently responding to 10 mg, further dose escalation is not justified.

None found for the use of Octreotide/Lanreotide for dumping syndrome or faecal incontinence

http://www.hsc.nihr.ac.uk/

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