Liraglutide

For obesity, not just type 2 diabetes

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Liraglutide was recently TGA approved as an adjunctive therapy for obesity, extending its indications for use beyond treatment of type 2 diabetes. What is its place in helping patients achieve and maintain weight loss?

The chronic nature of obesity has led to renewed interest in pharmacotherapy as an adjunct to lifestyle intervention for achieving and maintaining weight loss. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that was previously TGA approved for the treatment of type 2 diabetes, at a dose of 1.8 mg daily. In December 2015, the TGA approved a liraglutide product with a higher daily dose (3 mg) for the treatment of obesity. The 3 mg product has potential as a long-term obesity therapy, although there are currently limited long-term safety and efficacy data.

MedicineToday 2016; 17(5): 69-71

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The weight loss effects of the 3 mg liraglutide product appear superior to those of orlistat, the only other approved long-term obesity pharmacotherapy. The 3 mg liraglutide product can be prescribed by GPs, although the cost of a private prescription ($387 per month) may prove prohibitive for many patients.

What is liraglutide?

Liraglutide is an analogue of human GLP-1, a hormone that suppresses appetite and stimulates insulin secretion. Weight loss with liraglutide appears to be due to reduced appetite and energy intake.[1] Peripherally, GLP-1 receptor agonists slow gastric emptying, causing early satiety. Gastrointestinal adverse effects associated with these agents, such as nausea and vomiting, also contribute to reduced appetite.[2,3]

Weight loss associated with GLP-1 receptor agonists can, however, occur in the absence of nausea and vomiting and independent of delayed gastric emptying.[4] Recent studies suggest that the weight loss effects of liraglutide may therefore be predominantly mediated through its action within the central nervous system, as liraglutide is able to cross the blood–brain barrier.[5,6] This central induction of satiety may explain the greater weight loss effects seen with liraglutide compared with other larger nonpeptide GLP-1 receptor agonists.

What is the evidence?

Trials of the lower-dose liraglutide product in treatment of patients for type 2 diabetes consistently found it to be associated with modest weight reduction.[7,8] This finding led to three recent trials in adults with obesity or overweight without diabetes, which confirmed a dose-dependent weight reduction with liraglutide.[9-11]

In a recent 56-week randomised placebo-controlled trial involving more than 3700 adults, the 3 mg liraglutide product in conjunction with lifestyle intervention was associated with a mean 8.4 kg reduction in body weight, compared with 2.8 kg for placebo (lifestyle intervention alone) – i.e. a 5.6 kg mean-subtracted weight

1. CRITERIA FOR USE OF LIRAGLUTIDE (3 MG DAILY)

- BMI of 30 kg/m^2 or higher
- BMI in the range 27 to less than 30 kg/m^2 plus at least one weight-related comorbidity (e.g. dysglycaemia, hypertension, dyslipidaemia or obstructive sleep apnoea)

Abbreviation: BMI = body mass index.

2. ADVERSE EFFECTS OF LIRAGLUTIDE (3 MG DAILY)

Common

- Nausea and vomiting
- Diarrhoea or constipation
- Headache
- Hypoglycaemia

Less common

- Acute pancreatitis
- Dyspepsia, abdominal pain, gastro-oesphageal reflux, gastritis
- Renal impairment
- Fatigue
- Dizziness
- Insomnia
- Depression, suicidal ideation
- Allergic and injection site reactions
- Pancreatic cancer

loss with liraglutide.[12] Among those receiving liraglutide, 63% lost at least 5% of their initial body weight, and 33% lost at least 10%, compared with 27% and 11%, respectively, of those receiving placebo. Liraglutide was also associated with a significant improvement in cardiometabolic risk factors, including waist circumference, blood glucose level, blood pressure and sleep apnoea.[12]

Two of the recent trials in obese and overweight adults without diabetes directly compared liraglutide (at varying doses) with orlistat in conjunction with lifestyle intervention as well as with placebo (i.e. lifestyle intervention alone).[10,11] In the earlier of these trials, the mean weight loss with liraglutide was 4.8 kg (for the 1.2 mg dose), 5.5 kg (1.8 mg dose), 6.3 kg (2.4 mg dose) and 7.2 kg (3 mg dose), compared with 4.1 kg for orlistat and 2.8 kg for placebo.[10] A follow-up one-year open-label extension study assessed the safety and efficacy of higher-dose liraglutide (initial maintenance dose of 2.4 mg subsequently increased to 3 mg) compared with orlistat. After two years, those taking liraglutide 2.4/3.0 mg sustained a mean weight loss of 7.8 kg from baseline, 3.0 kg greater than the orlistat arm and unchanged from the end of the first year.[11]

In comparison, phentermine, which is an option for short-term (less than three months) weight management therapy in conjunction with lifestyle modification, is associated with weight loss that is approximately 3.6 kg greater than with placebo (95% confidence interval, 0.6 to 6.0 kg). Phentermine is contraindicated in patients with significant cardiovascular or psychiatric disorders.[13]

At present no head to head trials have compared the 3 mg liraglutide product with bariatric surgery, which overall remains the most effective weight loss intervention. It remains to be seen whether the 3 mg liraglutide product may have a role in patients in whom bariatric surgery has failed or is not appropriate.

When is liraglutide used?

The 3 mg liraglutide product is TGA approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults. Criteria for its use are shown in Box 1.

The 3 mg liraglutide product appears more effective than orlistat, which is also TGA approved for chronic weight management. However, unlike orlistat it is not PBS listed, limiting its accessibility. Orlistat also has longer-term safety and efficacy data available.

How is liraglutide used?

Liraglutide is injected once daily subcutaneously into the abdomen, thigh or upper arm. To minimise the gastrointestinal adverse effects, liraglutide should be initiated at 0.6 mg daily for one week and increased by 0.6 mg daily at weekly intervals until the maximum 3 mg daily dose is achieved.

GPs should keep in mind the 'stopping rule' for the 3 mg liraglutide product for obesity treatment: treatment should be discontinued after 12 weeks on the maximum 3 mg daily dose if the patient has not lost at least 5% of their body weight. Given the lack of long-term safety and efficacy data, therapy continuation should be re-evaluated at this time (i.e. week 16 after treatment initiation) and in an ongoing manner thereafter.

As the 3 mg liraglutide product is approved for chronic weight management, it seems reasonable for patients to continue therapy until they have lost 5 to 10% of their baseline body weight and potentially longer if there is evidence of further and/or durable weight loss associated with treatment. In practice, treatment duration with the 3 mg liraglutide product will ultimately be determined by its cost. Postmarketing studies assessing its longer-term safety will also provide further guidance on treatment duration.

There is no evidence at present for the efficacy of re-commencing the 3 mg liraglutide product for patients who regain weight after treatment cessation. However, it seems reasonable to speculate that reintroducing liraglutide treatment might be of benefit, although there may be a role for alternative interventions, including bariatric surgery.

Adverse effects of liraglutide

Liraglutide is commonly associated with gastrointestinal adverse effects that are generally self-limiting, including nausea and vomiting and diarrhoea or constipation (Box 2). Other frequent adverse effects are hypoglycaemia, particularly in patients with type 2 diabetes, and headache.[12]

Uncommon adverse effects of liraglutide include acute pancreatitis and other gastrointestinal effects, such as dyspepsia, abdominal pain, gastro-oesophageal reflux and gastritis. An increased incidence of pancreatic cancer is being noted in ongoing studies of GLP-1 receptor agonists. Renal impairment due to severe dehydration from nausea and vomiting have also been reported. Liraglutide is also associated with central effects, including fatigue, dizziness, insomnia, suicidal ideation and depression.[14] Allergic and injection site reactions can also occur.

Precautions

It is important to note that there are no long-term safety data for the 3 mg liraglutide product. For example, it is associated with an increase in heart rate, but the effects on cardiovascular morbidity and mortality have not been established.

Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2, because of an increased incidence of thyroid C-cell tumours observed in rodents.[15] It is also contraindicated in those with hypersensitivity or a history of angioedema to other GLP-1 receptor agonists and in pregnancy.

The 3 mg liraglutide product is not indicated for the treatment of type 2 diabetes and should not be used in combination with other GLP-1 receptor agonists or with insulin. It has not been studied in patients with a history of pancreatitis.

Conclusion

It is well recognised that weight reduction of 5 to 10% from baseline reduces cardiometabolic morbidity and mortality and improves quality of life in patients who are overweight or obese. Although weight loss can be achieved through lifestyle interventions, maintenance of weight loss remains difficult. Liraglutide is the first GLP-1 receptor agonist to be approved as obesity pharmacotherapy. It achieves superior weight loss compared with the only other long-term obesity pharmacotherapy, orlistat. The acceptability, durability of effect and long-term safety of liraglutide for weight loss remain to be seen. Moreover, as liraglutide is not PBS approved, GPs may find the cost prohibitive for their patients. MT

References

1. Van Can J, Jensen CB, Flint A, Blaak EE, Saris WHM. Effects of once daily GLP-1 analog liraglutide on gastric emptying, glycaemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond) 2014; 38: 784-793.
2. Flint A, Raben A, Ersboll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. Int J Obes (Lond) 2001; 25: 781-792.
3. Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulin-dependent) diabetic patients. J Clin Endocrinol Metab 1996; 81: 327-332.
4. Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. Diabetes 2011; 60: 1561-1565.
5. Sisley S, Gutierrez-Aguilar R, Scott M, D'Alessio DA, Sandoval DA, Seeley RJ. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. J Clin Invest 2014; 124: 2456-2463.
6. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest 2014; 124: 4473-4488.
7. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009; 373: 473-481.
8. Vilsboll T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. Diabetes Care 2007; 30: 1608-1610.
9. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013; 37: 1443-1451.
10. Astrup A, Rossner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009; 374: 1606-1616.
11. Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond) 2012; 36: 843-854.
12. Pi-Sunyer X, Astrup A, Fujioka K, et al; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015; 373: 11-22.
13. Li Z, Maglione M, Tu W, Mojica W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med 2005; 142: 535-546.
14. US Food and Drug Administration. Medication guide Saxenda® (sax-end-ah) (liraglutide [rDNA origin]) injection. Available online at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM487804.pdf (accessed May 2016).
15. US Food and Drug Administration. FDA approves weight-management drug Saxenda [press release]. 23 December 2014. Available online at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427913.htm (accessed May 2016).

COMPETING INTERESTS: Dr Sweeting received an Australasian Diabetes in Pregnancy Society clinical research grant sponsored by Novo Nordisk in 2014. Professor Caterson has participated in clinical trials of liraglutide, and his institution has received funding for this. He also has received conference registration and accommodation to present the results of these trials at a scientific meeting and has given a talk on obesity for Novo Nordisk.