Most patients with type 2 diabetes baulk at the idea of self-administering injections for the management of their diabetes. This is not simply because of their fear of needles. The additional burdens of adherence, titration, monitoring, inflexibility, hypoglycaemia and weight gain also limits the uptake of and compliance with insulin therapy.
But, not all injectables carry these limitations. In particular, the advent of Glucagon-Like Peptide-1 Receptor agonists (GLP-1R agonists) like exenatide and liraglutide, has changed the approach to injectable therapy in type 2 diabetes. In this article we look at the potential benefits and challenges of GLP-1R agonists for the management of type 2 diabetes in Australian general practice.

**What are Incretins?**

Over one hundred years ago, Moore and colleagues discovered that the intestine released hormones that regulated the functions of the pancreas and could lower glucose levels in people with diabetes. In 1929, Le Barre purified the glucose lowering element from gut extracts and called them incretins for INtestine seCREtion of INsulin. However, we are only now realising just how important this incretin pathway is. On average, two thirds of the insulin made by the pancreas in response to a meal is due to our incretin amplification system. Incretins also stimulate β-cell proliferation and/or reduce apoptosis and improve glucose sensitivity in β-cells that are sub-optimally responsive.

**What does GLP-1 do?**

The human body makes a number of incretins. In terms of glucose control, the most important of these is glucagon-like peptide-1 (GLP-1). Every time a meal is eaten, the L-cells of the intestine release GLP-1. These L-cells are found throughout the length of the intestine but are in highest concentration in the distal small intestine, ileum and colon. The initial stimulus to release GLP-1 is neurogenic, and probably mediated by activation of the vagal nerve. Subsequently, the passage of nutrients to the distal intestine triggers a further and larger GLP-1 release. The dramatic increase in GLP-1 after gastric bypass surgery is partly explained by the facilitation of the transit of nutrients to the distal intestine which is rich in L-cells.

GLP-1 exerts its glucose-lowering actions through activating a specific receptor, the GLP-1 receptor (GLP-1R). Exactly where this happens is unclear, but cells of the portal system, the liver and the β-cells of the pancreas all have GLP-1R. Incretins do not stimulate the production of insulin on their own (unlike sulphonylureas), rather they amplify any response, in a glucose-dependent manner. This so-called ‘incretin effect’ is reduced by approximately half in type 2 diabetes, contributing to poor post-prandial glucose control. GLP-1 levels are normal in type 2 diabetes (although they should be high given their glucose levels). By contrast, there is marked down-regulation of GLP-1 receptor and reduced sensitivity to its actions, which means that pharmacological levels, well above the normal range, are therefore required to overcome it.

Patients with type 2 diabetes inappropriately make over thirty grams of extra glucose every day, even though their glucose levels are already elevated. This so-called ‘anarchic gluconeogenesis’ explains how glucose levels can remain high even when fasting. GLP-1 not only increases insulin production but also suppresses the production of glucagon by the α-cells of the pancreas and therefore also suppresses gluconeogenesis and reduces fasting hyperglycaemia. This is just like the metabolic response to a large meal which suppresses unnecessary glucose production at a time when abundant glucose is being absorbed.

**How to Get More GLP-1?**

GLP-1 made by the intestine is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). Less than a quarter of the GLP-1 leaving the intestine ever reaches the liver. Even less (~10–15%) of newly secreted GLP-1 reaches the systemic circulation and only a fraction of this is in its intact active form. So inhibiting the DPP-4 enzyme with drugs known as “gliptins” is one way to increase GLP-1 levels.

An alternative approach is to inject a peptide that is resistant to DPP-4, but retains its potency at the GLP-1R. These so called GLP-1R agonists include exenatide and liraglutide.

**GLP-1 and the Gila Monster**

Exenatide is a synthetic form of exendin-4, a naturally occurring peptide originally isolated from the saliva of the lizard *Heloderma suspectum*.
Exenatide has glucose levels in the normal range. Counter-regulatory responses can keep hypoglycaemia more likely (unless background therapy is carefully down titrated).

What about Weight Loss?

Weight control is a pivotal component of diabetes management. Most people with type 2 diabetes are obese, and many are extremely so. GLP-1R agonists are able to induce useful weight loss, on average by ~2-3 kg or a 1kg/m² reduction in BMI over a year. GLP-1 agonists are not currently indicated for weight loss in Australia, although the FDA and the EU have approved liraglutide as a treatment option for chronic weight management in addition to a reduced-caloric diet and increased physical activity.

What about Nausea?

GLP-1 also acts to slow stomach emptying, in what has become known as the ‘ideal break’, a feedback mechanism that slows digestion to optimise nutrient absorption. Slowing the delivery of carbohydrate may be beneficial for glucose control and reduce insulin levels post-prandially, for the same reasons that a low GI diet may also have these benefits.

What about Hypoglycaemia?

Because incretins are amplifiers not stimulators of insulin release (unlike sulphonylureas), GLP-1R agonists only work when there is a stimulus for insulin release, like a meal or having high glucose levels. But if glucose levels are low, there is no signal to make insulin, so there is no incretin effect and little or no risk of hypoglycaemia when used on their own or in combination with other agents that do not cause hypoglycaemia, like metformin. In addition, they don’t suppress glucagon when glucose levels are low; so natural counter-regulatory responses can keep glucose levels in the normal range. However, when used in combination with sulphonylureas or insulin, GLP-1R agonists can sometimes make hypoglycaemia more likely (unless background therapy is carefully down titrated).

What about the Needles?

All GLP-1R agonists need to be injected as they are peptides that would not withstand the proteolytic environment of the gut. Injection is done under the skin of the thigh or abdomen twice daily for exenatide, or once daily for liraglutide. Acquiring needles is the same as for insulin. The injection technique is straightforward and less variable than insulin. Some people complain of bruising or pain at injection sites, but nodules or lipoatrophy are less common than with insulin injections. Most fears of injection are allayed once the reduced potential for hypoglycaemia and potential for weight loss have been explained.

What about Pancreatitis?

Because GLP-1 may cause proliferative changes in pancreatic duct cells it has long been believed that GLP-1R agonists may be associated with an increased risk of pancreatitis. The FDA and European Medicines Agency reported in 2013 that assertions regarding a causal association between incretin-based diabetes therapies and pancreatitis “are inconsistent with the current data.” However, more recent data support the warning of an increased risk of pancreatitis. However, this risk is small in absolute terms.
What about Cancer?

The shadow of cancer has recently been cast across many new agents for managing diabetes, including oral therapies and insulin. Today, every new agent must go through rigorous testing to ensure the risk of cancer is not modified, and GLP-1R agonists are no exception. Large clinical trials of GLP-1R agonists have not reported any increase in any cancers, and specifically no increase in cancers of the pancreas or the intestine. However, incretins have the potential to promote the growth of the rare medullary carcinoma of the thyroid (MCT) and GLP-1R agonists are contraindicated in patients with a personal or family history of MCT or multiple endocrine neoplasia type 2.

What about Heart Attacks?

Heart attacks and strokes account for over two thirds of all deaths in people with type 2 diabetes. Reducing the risk of cardiovascular events is a priority of diabetes management. Despite being available for over ten years, as yet cardiovascular outcome studies for the GLP-1R agonists are still ongoing, some of which may be reported soon. Overall accumulated data suggests that both these agents are safe, and do not pose a cardiovascular risk.

When to use a GLP-1R Agonist?

Intensifying glycaemic control while mitigating its risks continues to be a major challenge in primary care. Basal insulin provides good control of fasting glucose and HbA1c. However, its utility in the control of postprandial glucose excursions is limited and insulin often exposes patients to a cycle of weight gain and hypoglycaemia.

As an alternative strategy, GLP-1R agonists provide comparable control, but at reduced risk of hypoglycaemia and consistent benefit of weight loss. Exenatide is subsided by the PBS for combination therapy with metformin or a sulphonylurea when their combination is contraindicated or must not have been tolerated. It can also be used for triple therapy in patients with suboptimal glucose control despite treatment with maximally tolerated doses of metformin and a sulfonylurea. Currently, there is no PBS subsidy for combination therapy with basal insulin, although this is an attractive alternative adding short acting insulin in this setting.

Competing interests: MCT has received honoraria for educational symposia conducted on behalf of Astra Zeneca, BMS and the Boehringer Ingelheim and Lilly alliances, both manufacturers of GLP-1R agonists.

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