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DPP-4 Inhibitors Conceptualising a New Approach to Diabetes Management

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DPP-4 Inhibitors
Conceptualising a New Approach to Diabetes Management

Merlin Thomas

Most patients with type 2 diabetes will need more than monotherapy to achieve targets for glucose control. Dual therapy may come early in their management when it is clear that monotherapy is insufficient (primary failure) or later as the efficacy of therapy gradually wanes (secondary failure). But dual therapy will eventually come to over 90% of our clients. There are many different strategies that can be used as second-line for glucose control in type 2 diabetes.

References:

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When using metformin as the first-line agent, standard practice has been until recently to add on a sulphonylurea. However, over the last decade the percentage of patients following this track in Australia has halved, chiefly due to hypoglycaemia, weight gain and the need for dose-titration in patients who are increasingly old, frail and/or have complicated conditions. While at the same time, new glucose lowering agents without these potential impacts have emerged as alternatives. In this article we will look at the potential benefits and challenges of DPP-4 inhibitors as second-line agents for the management of type 2 diabetes in Australian general practice.

Incretins and DPP-4

Incretins are natural hormones that are made by the intestine in response to a meal.[1] They represent an important means to communicate the size of a meal and coordinate a proportional metabolic response to it. One of their actions is to amplify the amount of insulin released from the pancreas after a meal. In much the same way as an amplifier makes a proportionally louder sound come out of a speaker, the bigger the glycaemic load (signal) the greater the amplification of pulsatile insulin production (**FIGURE**).

On average, two thirds of the insulin made by the pancreas in response to a meal is due to the incretin amplification system.[1] However, this '*incretin effect*' is reduced by approximately half in patients with type 2 diabetes.

The human body has a number of incretin hormones, the most important of which is *glucagon-like peptide-1* (GLP-1). However, its effect is limited, partly because of the enzyme DPP-4 that breaks it down. Inhibiting the DPP-4 enzyme with drugs known as "*gliptins*" means that incretins including GLP-1 can persist long enough and in high enough levels to better amplify insulin secretion. On average GLP-1 levels are 2-4 fold higher in patients using DPP-4 inhibitors.

Because incretin levels are supposed to correlate with the size of a meal, the higher incretin levels achieved following DPP-4 inhibitors essentially tricks the pancreas to respond as if any meal was larger than it really was, and should therefore mount a proportionally greater insulin response. This has roughly the same effect as injecting an incretin, reducing the HbA1c by 0.5-1% on average in most patients.[2]

However, a key advantage of gliptins is that they are taken in tablet form, once, or at the most, twice daily, without titration. They can also be taken any time of the day, with or without food and do not require coordination with meals or physical activity.

Because the response to DPP-4 inhibitors is proportional, its actions are well suited to patients with a variable lifestyle, who don't eat the same amount or type of food every day, or who exercise irregularly. For example, its actions are greatest with a bigger meal, but if one day the meal is small or glucose levels are lower because of undertaking exercise, a proportionally lower response is co-ordinated.

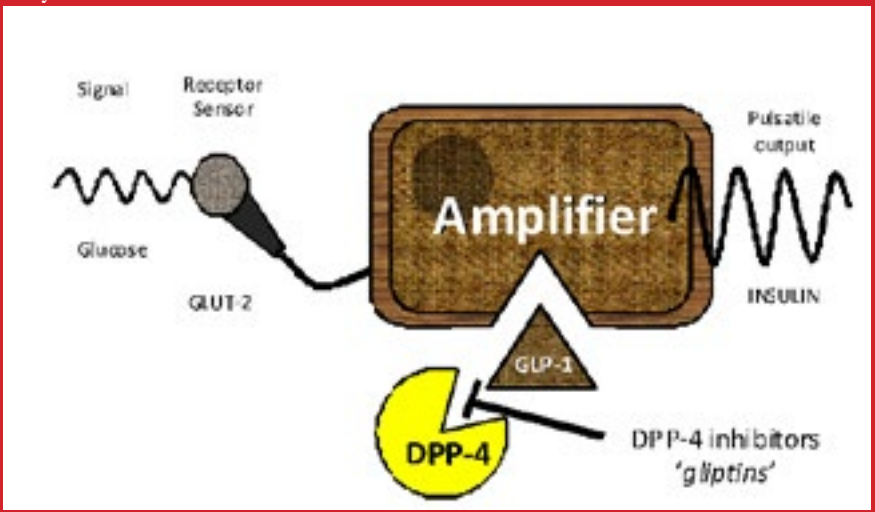
Incretins and fasting glucose

Patients with type 2 diabetes inappropriately make over thirty grams of extra glucose every day, even though their glucose levels are already elevated.[3] This is one reason why glucose levels can remain high even when fasting. Incretins not only increase insulin production but they also suppress the production of glucagon by the pancreas and its subsequent effect of stimulating gluconeogenesis. This is just like the (appropriate) metabolic response to a large meal which suppresses unnecessary glucose production at a time when abundant glucose is being absorbed. Through the elevation of natural incretin levels, DPP-4 inhibitors reduce anarchic gluconeogenesis in type 2 diabetes and improve control of fasting as well as post-prandial glucose levels.[3]

What about exhaustion?

Long-term treatment with sulph-onylureas is associated with a progressive loss of its efficacy. This is thought to be due to exhaustion and loss of beta cell function. By contrast, incretins are thought to protect beta cells and their functions. Moreover, although incretins increase insulin, they do so in a proportional manner, so that mean insulin levels fall (as glucose levels fall). Together this makes glucose lowering with DPP-4 inhibitors potentially sustainable than with sulphonylureas, which can be important for younger patients in whom a long treatment course is anticipated and secondary failure represents a major setback.

Figure: Glucose-stimulated insulin release from the beta cell is amplified by GLP-1. These actions can be enhanced following inhibition of DPP-4, the enzyme that metabolises GLP-1



What about hypoglycaemia?

Incretins do not stimulate the production of insulin on their own (unlike sulphonylureas). Incretins are only amplifiers. This means that DPP-4 inhibitors only work when there is a stimulus for insulin release, like a meal or having high blood 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 essence, you can't amplify zero. In addition, DPP-4 inhibitors don't suppress glucagon when glucose levels are low, so natural counter-regulatory responses can keep glucose levels in the normal range. However, in patients already taking sulphonylureas or insulin, any improvements in glycaemic control achieved when adding on DPP-4 inhibitors can sometimes make it more likely that hypoglycaemia will be induced by sulphonylureas or insulin. Often a proactive reduction in insulin or sulphonylurea is warranted to avoid this risk.

What about weight gain?

DPP-4 inhibitors do not cause weight gain.[4,5] This can be valuable in early diabetes when weight loss is a high priority, and can be hard to achieve, reinforce or sustain with sulphonylureas, which cause an average weight gain of 1-2 kg in the first 6 months of therapy.[6] By contrast, GLP-1 agonists can cause weight loss. Why DPP-4 inhibitors don't produce weight loss, while the incretins they elevate are associated with weight loss is unclear, but may relate to the high levels of incretins achieved when injecting and their effects on stomach emptying. This also causes nausea and vomiting in some patients, symptoms not seen with DPP-4 inhibitors.

What about kidney disease?

Every class of glucose lowering medication has challenges in patients with chronic kidney disease (CKD) from metformin and lactic acidosis to sulphonylureas with accumulation and an increased risk of hypoglycaemia. SGLT-2 inhibitors lose efficacy in patients with CKD. By contrast, DPP-4 inhibitors retain their efficacy and safety across all levels of kidney function, making them an ideal agent in this complex setting. Some DPP-4 inhibitors require dose adjustment in patients with renal impairment to ensure drug exposure remains consistent in all patients regardless of renal function. This has nothing to do with the renal safety of these agents.

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 DPP-4 inhibitors are no exception. Large clinical trials of DPP-4 inhibitors have not reported any increase in any cancers, and specifically no increase in pancreatitis or cancers of the pancreas or the intestine.[4,7] However, incretins have the potential to promote the growth of the rare medullary carcinoma of the thyroid (MCT) and DPP-4 inhibitors are contraindicated in patients with a personal/family history of MCT or multiple endocrine neoplasia 2.[8]

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. Even if an agent improves glucose control, if it increases the risk of cardiovascular disease, as was the case with rosiglitazone, it has no place in contemporary diabetes care. The United States Food and Drug Administration (FDA) now mandates that all new diabetes agents undergo rigorous testing to demonstrate cardiovascular safety. Again DPP-4 inhibitors are no exception. Overall accumulated data suggests that both these agents are safe, and do not pose a cardiovascular risk.[4,9] Large scale clinical trials with DPP-4 inhibitors support this conclusion.[7] A question mark still hangs over whether DPP-4 inhibitors increase the risk of heart failure in susceptible paients,[10] although their use is not contraindicated in patients with heart failure and there are some data to support the value of incretins in this setting.

When to use a DPP-4 inhibitor?

DPP-4 inhibitors are not more effective than other glucose lowering agents, and lower the HbA1c roughly similar in magnitude to what can be achieved with other glucose lowering agents such as metformin, sulphonylureas, thiazolidinediones and SGLT-2 inhibitors.11 However, of all glucose lowering agents they are the best tolerated, and don't need to be titrated. This makes their use comparatively easy, and has led to gliptins being widely used as the second-line agent of choice in patients with complications in whom first doing no harm is top priority.

Competing interests:

MCT has received honoraria for educational symposia conducted on behalf of Astra Zeneca, BMS Boehringer Ingelheim, Lilly, MSD and Takeda, all marketers of DPP-4 inhibitors.

Annual Scientific Meeting

26 - 28
August 2015

Adelaide Convention Centre,
South Australia

Travel Grant and Registration available

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"Shake it up: A fresh perspective on the science of diabetes"

Key Dates

Abstract Submission Deadline – **Monday 1 June 2015**
Early Bird Registration Deadline – **Monday 29 June 2015**
Abstract Notifications – **Monday 29 June 2015**
Travel Grant Application Deadline – **Monday 29 June 2015**

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