Dipeptidyl peptidase-4 inhibitors: their role in the management of type 2 diabetes

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Abstract

The production of glucagon-like peptide 1 (GLP-1), an incretin hormone, has been shown to be abnormally low in patients with type 2 diabetes, suggesting that GLP-1 may be a contributor in the pathogenesis of the disease. New type 2 diabetic medications target incretin hormones in their mechanism of action. The incretin effect is based on the understanding that oral glucose has a greater stimulatory effect on insulin secretion than that of intravenous glucose. Over the past few years, a number of therapeutic agents, acting either as incretin mimetics, e.g. GLP-1 agonists, or inhibitors of the breakdown of GLP-1, e.g. dipeptidyl peptidase-4 inhibitors, have become available as treatment options for the management of type 2 diabetes.

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Introduction

It is estimated that 6.5% of adults aged 20-79 years have type 2 diabetes in South Africa. An age-adjusted prevalence of up to 13% has been described in urban populations.1 The effects of urbanisation, lack of exercise and unhealthy eating habits have been found to be important contributors to the rising prevalence of type 2 diabetes, as well as obesity, in the country.[1]

Type 2 diabetes is a progressive disease which may require intensification of therapy over time. Management includes a prudent diet, regular exercise and medicine to reduce blood glucose levels. Current pharmacological options in the management of type 2 diabetes include sulphonylureas, insulin, thiazolidinediones, α-glucosidase inhibitors and metformin. These treatment options, although highly effective in reducing blood glucose levels, may be associated with an increased risk of hypoglycaemia, as seen with sulphonylureas and insulin; weight gain, as noted with insulin, sulphonylureas and thiazolidinediones; and gastrointestinal intolerance, as observed with metformin. These unwanted adverse effects may act as barriers to optimal glycaemic control.[2]

As a result, newer and safer treatment options for optimal glycaemic control are continuously being investigated and developed. The glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are examples of such development.

This article will focus on the DPP-4 inhibitors, also known as the "gliptins", and their place in therapy in the management of type 2 diabetes.

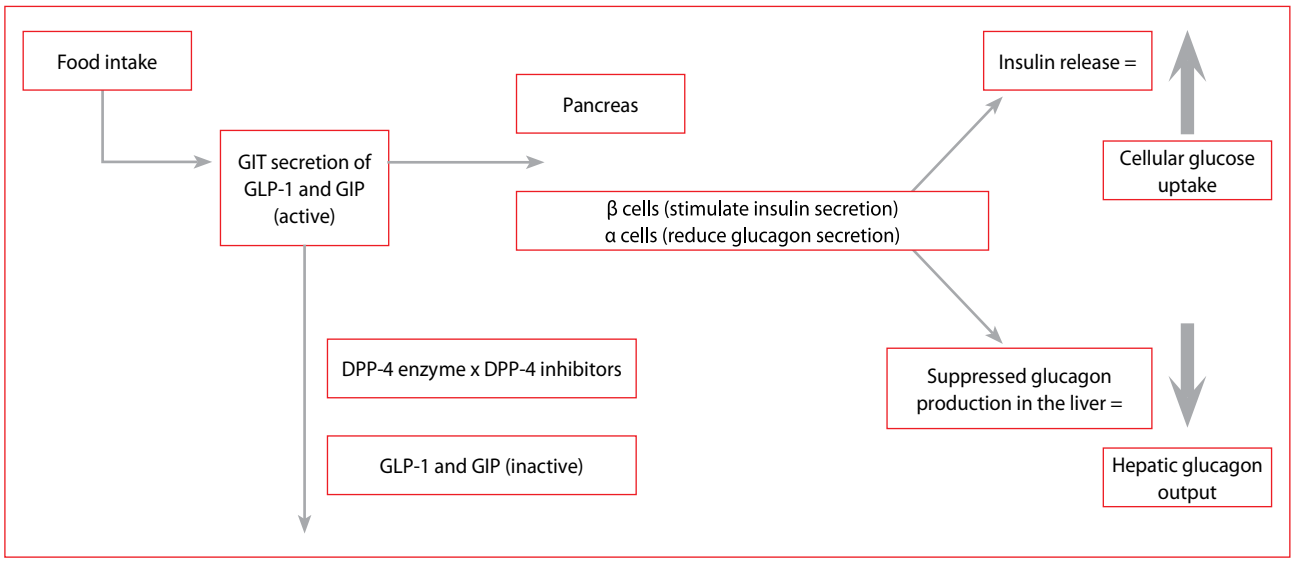
A closer look at dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors are a new class of medicine that work to potentiate the effect of incretin hormones. Incretin hormones are secreted from the gastrointestinal tract (the enteroendocrine cells), into the bloodstream in response to food intake. The two most well-characterised incretin hormones are the GLP-1 and glucose-dependent insulinotopic polypeptide, also known as gastric inhibitory peptide (GIP). GLP-1, in particular, appears to be responsible for the majority of the incretin effects on the pancreatic .-cell function.[2,3]

When blood glucose levels are elevated following a meal, GLP-1 is released from the gastrointestinal tract, and it:

- Stimulates insulin secretion from the pancreatic β cells.
- Reduces glucagon secretion from the pancreatic α cells.
- Improves β-cell function.
- Slows gastric emptying.[2,3]

Circulating levels of GLP-1 are low in the fasting state, and rise quickly following a meal. However, GLP-1 has a very short half-life and is rapidly degraded by the enzyme, DPP-4.[2-6] In an attempt to harness the beneficial effects of GLP-1, research has focused on interventions along the GLP-1 pathway. The result of this research has been



DPP-4: dipeptidyl peptidase-4, GIT: gastrointestinal, GIP: gastric inhibitory peptide, GLP-1: glucagon-like peptide 1

Figure 1: Schematic representation of the mechanism of action of dipeptidyl peptidase-4 inhibitors

the development of GLP-1 agonists, e.g. exanetide and liraglutide, as well as the DPP-4 inhibitors.

GLP-1 agonists have a protein-based structure, and although they have a longer half-life than endogenous GLP-1, they require parenteral administration as is the case with exenatide (Byetta®) and liraglutide (Victoza®). Both of these are available as pen devices.[1,3,4,7]

In contrast to this, DPP-4 inhibitors are smaller molecules that can be absorbed intact from the gastrointestinal tract, making oral administration possible.[3]

Figure 1 is a schematic representation of the mechanism of action of DPP-4 inhibitors.

Despite their common mechanism of action, the DPP-4 inhibitors show marked differences in their chemical structure.[2,4,6] This may explain some of the variance in the pharmacokinetic profiles of these products.

Drug interaction profile

In general, DPP-4 inhibitors do not interfere with cytochrome P450 (CYP) enzymes. They are neither inhibitors nor inducers. The exception is saxagliptin (Onglyza®), which is metabolised by the CYP3A4/5 isoform into a primary active metabolite.[8,9] As a result, saxagliptin may require dosage adjustment if taken concurrently with CYP3A4/5 inhibitors, such as ketoconazole, itraconazole, indinavir, nelfinavir, ritonavir and saquinavir.[1,8,10]

The absence of significant drug-drug interactions with this class of medicine can be explained by their favourable pharmacokinetic characteristics and their low plasma-protein binding.[4,8,10]

Safety profile

DPP-4 inhibitors have been generally well-tolerated in short-term studies. Common reported adverse effects include nasopharyngitis (inflammation of the nasal passages), urinary tract infections, pancreatitis and headaches. Serious allergic reactions have been reported, including anaphylactic reactions, angioedema and exfoliative dermatological reactions.[1-5] The incidence of hypoglycaemia is low, but may be increased when DPP-4 inhibitors are used in combination with other antidiabetic agents. The DPP-4 inhibitors also appear to be less likely to be associated with weight gain.

Since these products are fairly new on the market, long-term, real-life experience with their use is needed to further confirm their safety profile.

Available dipeptidyl peptidase-4 inhibitors

Various DPP-4 inhibitors are at different stages of development and registration across the globe. These include sitagliptin, vildagliptin, alogliptin, saxagliptin and linagliptin.

Sitagliptin was the first of the DPP-4 inhibitors to be approved by the US Food and Drug Administration in 2006. This was followed by the approval of vildagliptin in February 2007. Saxagliptin (Onglyza®), vildagliptin (Galvus®) and sitagliptin (Januvia®) are currently available on the South African market.[7,9,11-13]

Table I lists some of the internationally available DPP-4 inhibitors.

The place of dipeptidyl peptidase-4 inhibitors in therapy

DPP-4 inhibitors are effective as monotherapy, and also in combination with other oral antidiabetic agents. Plasma DPP-4 inhibition profiles are consistent with once-daily dosing for all members of this class, with the exception of Galvus® .[2,8,10]

Table I: Internationally available dipeptidyl peptidase-4 inhibitors

Feature (Onglyza®)	Saxagliptin (Galvus)®	Vildagliptin* (Januvia)®	Sitagliptin*	Linagliptin	Alogliptin
Recommended dosage	5 mg once daily	50 mg twice daily (once daily when used in combination with sulphonylureas)	100 mg once daily	5 mg once daily	25 mg once daily
Indication	Adjunct to diet and exercise in adults with type 2 diabetes, either as monotherapy or in combination with other antidiabetic agents	Adjunct to diet and exercise in adults with type 2 diabetes, either as monotherapy or in combination with other antidiabetic agents	Adjunct to diet and exercise in adults with type 2 diabetes, either as onotherapy or in combination with metformin or a thiazolidinedione	Not registered in South Africa. (Approved by the FDA)	Not registered in South Africa. (Approved by the FDA)
Selectivity for DPP-4	Moderate	Moderate	High	Moderate	Moderate
HbA_{1c}-lowering effect	Similar efficacy (modest reduction 0.5-1.1%)	Similar efficacy (modest reduction 0.5-1.1%)	Similar efficacy (modest reduction 0.5-1.1%)	Similar efficacy (modest reduction 0.5-1.1%)	Similar efficacy (modest reduction 0.5-1.1%)
Use in renal impairment	Dosage adjustment is required in patients with moderate or severe renal impairment	Contraindicated in patients with moderate or severe renal impairment	Contraindicated in patients with moderate or severe renal impairment	No dosage adjustment	Dosage adjustment is required in patients with moderate to severe renal impairment
Use in hepatic impairment	Contraindicated in patients with moderate to severe disease	Contraindicated	Contraindicated in patients with severe disease	No dosage adjustment	No dosage adjustments are required in patients with mild to moderate hepatic impairment
Drug-drug interaction potential	Potential for interaction with strong CYP3A4/5 inhibitors e.g. ketoconazole	Low	Low	Low	Low

*Vildagliptin and sitagliptin are also available in combination with metformin as Galvus Met® and Janumet®, respectively, indicated as an adjunct to diet and exercise in patients with type 2 diabetes who are already stabilised on the combination of DPP-4 inhibitors and metformin.[12]
CYP3A4/5: cytochrome 3A4/5, DDP-4: dipeptidyl peptidase-4, FDA: US Food and Drug Administration, HbA_{1c}: haemoglobin A_{1c}

DPP-4 inhibitors are contraindicated when there is:

- Compelling indication for insulin therapy.
- A history of a serious hypersensitivity reaction to DPP-4 inhibitors.
- A patient with a history of acute pancreatitis, chronic or recurring pancreatitis, or pancreatic cancer.[1]

Conclusion

The development of DPP-4 inhibitors, which potentiate the incretin hormones by inhibiting the enzyme that is responsible for their degradation, has recently emerged as an approach that appears to be promising for the treatment of type 2 diabetes.

Although these agents have modest efficacy [they reduce haemoglobin A_{1c}(HbA_{1c}) by 0.5-1.1% compared to placebo], they represent an important class of compounds that provide an alternative to other traditional therapies that are used in the management of type 2 diabetes.[1] While they do not appear to lower glucose to a greater extent than existing therapies, when used alone, they offer the potential advantage of a low risk of hypoglycaemia and weight gain. As there is a low risk of hypoglycaemia developing with their use, they may be advantageous in patients who are close to achieving their target HbA_{1c}, but who continually experience elevated glucose levels following a meal.

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