The Incretin effect and the use of dipeptidyl peptidase IV inhibitors

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Hormones secreted by the entero-endocrine cells of the gut in response to the ingestion of nutrients are known to stimulate insulin secretion. The gluco-regulatory effects of these 'incretin' hormones are the basis for new therapies for type 2 diabetes. Drugs that inhibit Dipeptidyl peptidase IV, an enzyme that breaks down incretin hormones, have been shown to increase active levels and improve glycemic control. In clinical trials, DPP-IV inhibitors (or gliptins) have shown efficacy and tolerability in the management of hyperglycemia in type 2 diabetes, without causing significant weight gain or hypoglycemia. This present review evaluates the concept, therapeutic potential and limitations of DPP-IV inhibitors as anti-diabetic agents.

KEY WORDS: Type 2 diabetes, incretins, glucagon-like peptide-1, dipeptidyl peptidase IV inhibitors

Introduction

Diabetologists have known for some time that there are multiple signals from the gastro-intestinal tract to the pancreas. A classic experiment from the 1960s compared the metabolic response to a glucose load delivered intravenously versus intra-jejunally.[1] While serum levels of glucose were similar, the plasma insulin response to glucose administered directly to the gut was significantly greater. This has been termed the 'incretin effect' and has a corollary in nature with the 'Gila monster' (Heloderma Suspectum), a lizard which only eats four times a year and uses the incretin gut response to stimulate its dormant pancreas to produce insulin.[2]

In recent years, our understanding of the 'entero-insular' axis has led to the development of new treatments and this article explores the actions and issues surrounding the incretin effect, incretin hormones such as Glucagon-like peptide (GLP) and dipeptidyl peptidase (DPP) IV enzyme inhibition.

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Discussion

Understanding that there is an increased insulin response to oral administration of glucose as compared to parental administration has led to much research on the multiple signals from the gut to the pancreas and the implications of this for the treatment of diabetes. These signals include the metabolic response to absorbed nutrients, neural stimulation via the vagus nerve and endocrine signals to the gut, liver, brain and pancreas.[3] This has the effect of heightening nutrient-stimulated insulin secretion. The incretin effect mentioned above is mainly due to Gastric insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). These incretin hormones are normally released in response to a meal and their effects are outlined in Table 1.

Type 2 diabetes is a multi-factorial condition characterized by impaired insulin release and sensitivity. We know that there is a diminished incretin effect in diabetes and this

Table 1: Effects of incretin hormones

Pancreatic effects	Extra-pancreatic effects
Increased glucose dependent insulin secretion	Reduced hepatic insulin extraction
Increased pro-insulin biosynthesis	Reduced gastric acid secretion
Increased beta-cell survival	Increased satiety
Decreased glucagon secretion	Reduced body weight (chronic effect)
	Reduced gastric emptying rate
	Increased myocardial glucose extraction
	? Increased lipogenesis

is the reason behind the development of new treatments to enhance the body's metabolic handling of glucose via the manipulation of these hormonal pathways.

The use of exogenous GLP-1 (e.g, Exenatide, an incretin mimetic) to elevate the physiologic incretin effect has been documented elsewhere.[3,4] It involves twice daily subcutaneous administration or long-acting release once weekly injection and shows reductions in post-prandial glucose concentrations and HbA_{1c} by 1-2%, associated with weight loss (2-5 kg).[5] Many Diabetologists have argued that by resorting to regular subcutaneous injections, there is little difference to the patient with regards to insulin therapy. Much of the thrust of modern diabetes care, especially from the patient perspective, is in delaying the commencement of insulin therapy because of the dislike and inconvenience of regular injections. Therefore, if the strategy is to optimize glycemic control via oral therapy, then we should look at the work done on DPP IV inhibitors.

Dipeptidyl peptidase IV is the enzyme responsible for the degradation of GLP-1 and GIP. It rapidly inactivates them and indeed their half-lives are less than 2 mins.[6] This leads to the formation of metabolites that are devoid of insulin-releasing activity. Preventing the degradation of the incretin hormones by blocking the action of DPP IV has led to the creation of a new class of drugs known as 'gliptins'. Their mechanism of action is distinct from any existing class of oral glucose-lowering agents.

The leading DPP-IV inhibitors have shown clinically significant HbA_{1c} reductions up to 1 year of treatment and offer many potential advantages over existing diabetes therapies including a lower risk of hypoglycemia, minimal effect on body weight and the potential for regeneration of pancreatic beta cells based on animal and *in-vitro* studies.[7] The DPP IV inhibitors appear to have great potential for the treatment of type 2 diabetes, but only time will tell if this is to be realized. Sitagliptin (Januvia) is the first on the market in the UK and was only licensed in April 2007; therefore, clinical experience is limited. It is a once-daily oral dose for combination with metformin or glitazones and not yet indicated for monotherapy. It is mostly excreted unchanged by the kidneys. It involves active tubular secretion via OAT-3 and so renal function should be monitored and there are a few reported drug interactions, e.g, slight increase in digoxin levels.[8]

There are three major European clinical trials of phase 3 status which have demonstrated the effectiveness of gliptins. The mean HbA_{1c} reduction is 0.7% although much greater reduction is achieved in poorly controlled participants with HbA_{1c} >9.5%. Gliptins reduce fasting plasma glucose as well as postprandial glucose significantly and without any effect on weight. The first trial compared the combination of metformin and gliptin.[9] After a screening diet / exercise run-in period, a metformin dose titration / stabilization period and a 2-week, single-blind, placebo-controlled run-in period, 701 patients, aged 19-78 years, with mild to moderate hyperglycemia (mean HbA_{1c} 8.0%) receiving ongoing metformin (≥1,500 mg / day) were randomly assigned to receive the addition of placebo or sitagliptin 100 mg once-daily in a 1:2 ratio for 24 weeks. At week 24, sitagliptin treatment led to significant reductions in HbA_{1c} (–0.65%), fasting plasma glucose and 2-h post meal glucose compared to placebo. Fasting insulin, fasting C-peptide, fasting proinsulin-to-insulin ratio, post-meal insulin and C-peptide areas under the curve (AUCs), post-meal insulin AUC-to-glucose AUC ratio, homeostasis model assessment of β-cell function and quantitative insulin sensitivity check index were significantly improved with sitagliptin relative to placebo. A significantly greater proportion of patients achieved an HbA_{1c} <7% with sitagliptin (47.0%) than with placebo (18.3%). There was no increased risk of hypoglycemia or gastrointestinal adverse experiences with sitagliptin compared with placebo. During this study, patients underwent a standard 2-h meal tolerance test, enabling an assessment of the effect of treatment on post-meal glucose, insulin and C-peptide concentrations and the ratio of insulin to glucose. Treatment with sitagliptin led to clinically important and statistically significant improvements in all of these end points compared with placebo.

The second study compared glitazone plus gliptin combination to glitazone and placebo.[10] This was a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients aged ≥18 years. At screening, all patients began a diet / exercise program that continued throughout the study period. Patients taking hypoglycemic therapy other than pioglitazone underwent a washout of this therapy and entered an 8- to 14-week open-label pioglitazone dose-titration / stabilization period. Patients with an HbA1c ≥7% and ≤10% at the end of this period entered a 2-week, single-blind, placebo run-in period (total duration of run-in period, up to 21 weeks). Patients who had been receiving pioglitazone monotherapy (30 or 45 mg / d) and had an HbA_{1c} ≥7% and ≤0% entered the 2-week, single-blind, placebo run-in period directly. Thus, at the time of randomization, all patients were receiving ongoing pioglitazone (30 or 45 mg / d). Patients were randomized

in a 1:1 ratio to receive sitagliptin 100 mg once daily or placebo for 24 weeks. The primary efficacy end point was the change from baseline in HbA_{1c} at week 24. Secondary efficacy end points included the change from baseline in fasting plasma glucose (FPG), insulin and proinsulin; the Homeostasis Model Assessment beta-cell function and insulin-resistance indices; the proinsulin / insulin ratio; the Quantitative Insulin Sensitivity Check Index; the percentage changes from baseline in selected lipid parameters; the proportion of patients meeting the American Diabetes Association HbA_{1c}, goal of <7.0%; the proportion of patients requiring metformin rescue therapy; and the time to initiation of rescue therapy. 175 patients were randomized to receive sitagliptin and 178 were randomized to receive placebo. The mean (SD) baseline HbA_{1c} value was 8.1% (0.8) in the sitagliptin group and 8.0% (0.8) in the placebo group. After 24 weeks, sitagliptin added to pioglitazone therapy was associated with significant reductions compared with placebo in HbA_{1c} [between-treatment difference in least squares (LS) mean change from baseline –0.70%; 95% CI, –0.85 to –0.54; $P < 0.001$) and FPG (17.7 mg / dL; 95% CI, –24.3 to –11.0; $P < 0.001$). Mean HbA_{1c} values at end point were 7.2% (0.9) and 7.8% (1.1) in the respective treatment groups and the proportions of patients reaching a target HbA_{1c} of <7.0% were 45.4% and 23.0% ($P < 0.001$). Significant reductions in fasting serum pro-insulin levels and the pro-insulin / insulin ratio were seen with sitagliptin treatment compared with placebo (both, $P < 0.01$).

The third trial was perhaps the most interesting. Nauck and colleagues compared the combination of metformin plus gliptin against metformin plus sulphonylurea in type 2 diabetic patients inadequately controlled on metformin alone.[11] After a metformin dose titration / stabilization period (≥1500 mg / day), 1172 patients were randomized to the addition of sitagliptin 100 mg q.d. ($N = 588$) or glipizide 5 mg / day (uptitrated to a potential maximum 20 mg / day) ($N = 584$) for 52 weeks. While there was no significant difference between them in terms of glycemic control - both achieved an equivalent reduction in HbA_{1c} - there was a significant decrease ($P < 0.001$) in the number and frequency of hypoglycemic episodes in those patients on sitagliptin. Also, there was no weight increase in the patient group taking DPP-IV inhibitors compared with glipizide.

Taken together, these trials demonstrate that there are true and reproducible glucose-lowering effects in the long term using DPP-IV inhibitors and they are certainly suitable for combination use. Their effects are glucose-dependent and this significantly reduces the risks of hypoglycemia and the fact that they are weight-neutral, via the effect on satiety, makes them increasingly attractive. What we need more information on is whether they would be suitable as first line or monotherapy. There have been no direct comparisons with metformin and, perhaps, future studies should evaluate their HbA_{1c} lowering properties in a direct head-to-head trial of metformin versus gliptin on patients who have been found to be intolerant of metformin.

Safety and tolerability

Treatment with sitagliptin added to the ongoing metformin therapy is generally well tolerated. The overall incidence of clinical adverse experiences, drug-related clinical adverse experiences, serious clinical adverse experiences and drug-related serious clinical adverse experiences was similar in the different treatment groups in the trials performed so far. The incidence of discontinuation due to adverse experiences was also similar between the two treatment groups. There were no statistically significant differences in the incidence of either hypoglycemia or predefined gastrointestinal adverse experiences between the sitagliptin and placebo groups. Due to the glucose-dependent nature of the incretin hormones, insulinotropic effects do not occur during euglycemia or hypoglycemia.[12,13] Thus, the incidence of hypoglycemia is extremely rare, even in the fasting state.

Potential side effects of DPP-IV inhibition may result from the inadvertent inhibition of related enzymes. DPP IV is a cell-surface and circulating-peptidase enzyme and is also known as CD26 (a T-cell activating antigen). This has widespread expression throughout the gastro-intestinal tract, pancreas, kidneys, thymus gland and elsewhere and there is some debate regarding the role of DPP IV for normal immune function, but it appears that its absence can be compensated for.[14,15] So far, treatment with sitagliptin has not been associated with serious adverse events. Studies on cardiovascular outcomes are also needed.

Body weight

Studies on the gliptins, vildagliptin and sitagliptin have shown to be body weight-neutral in the long term.[16] With GLP-1 analogs, there is evidence to show a significant reduction in body weight. The difference between the two incretin therapies is probably due to the fact that supra-physiological concentrations can be obtained with GLP-1 analogs, whereas DPP-IV inhibitors support the physiological role of GLP-1 without reaching the higher doses required to induce a reduction in body

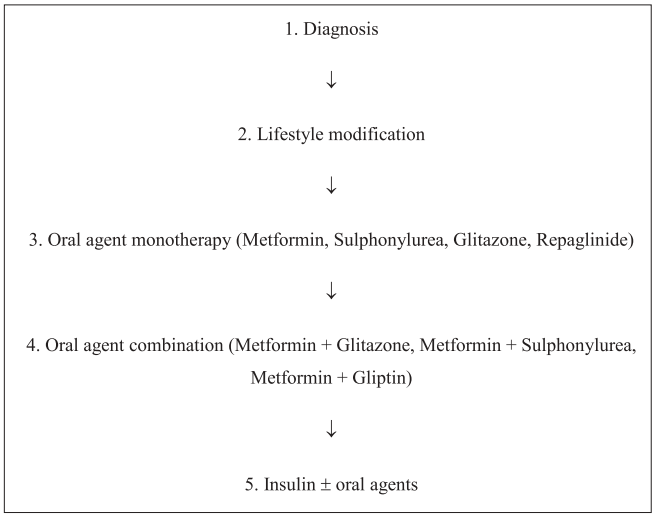

Figure 1: Treatment of type 2 diabetes (modified from ASA-EASD consensus algorithm 2006)[18]

weight.[17] However, weight neutrality is something to be admired when we have so much experience with problems relating to glitazones, sulphonylureas and insulin.

Conclusions

The incretin effect and DPP-IV inhibition are new targets in our battle against diabetes. Several large studies have shown the benefits of gliptins in enhancing the body's incretin response to nutrients and subsequently enhancing the action of insulin in a glucose-dependent manner. The benefits are sustained significant HbA1C reduction, limited hypoglycemia, weight neutrality and beneficial effects on beta-cell function. Compared to GLP-1 analogs, they have the advantage of oral administration and fewer GI side effects. Gliptins have been recommended for combination use [Figure 1], but it is still too early to say how effective they would be in patients with poorly controlled or long-standing disease. Clinical experience will as usual give us the best guide to stabilizing the diabetes epidemic.

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