Dipeptidyl peptidase-IV inhibitors: fixing type 2 diabetes?

The optimal treatment of type 2 diabetes is currently uncertain. This article reviews a new class of oral hypoglycaemic agents: dipeptidyl peptidase-IV inhibitors. By potentiating the action of incretins they offer a more 'physiological' control of blood sugar with fewer side effects, and the possibility of ameliorating the decline in beta cell function.

The World Health Organization estimates that the number of diabetics will rise from 194 million currently to 333 million by the year 2025 (International Diabetes Federation, 2003). The diabetic population of North America is predicted to grow by nearly 60% with increases of over 100% in Asian and Pacific nations (International Diabetes Federation, 2003). Underlying this epidemic in type 2 diabetes is a sedentary lifestyle and obesity. In the United States an estimated 40% of adults have the metabolic syndrome, which trebles the risk of developing diabetes (Ford, 2005).

While a major role exists for prevention through lifestyle modification (Hu et al, 2001; Knowler et al, 2002), this will require major political and social initiatives. In the short term it is likely to be easier to persuade a patient to take a tablet than to exercise. Thus medication, ideally for the prevention (or at least deferral) and treatment of diabetes, will have an increasing role to play.

The management of type 2 diabetes

Until recently medication in diabetes was directed at lowering blood sugar levels. Traditional agents such as insulin, the biguanides and sulphonylureas, while providing stable glucose control for some years, have little impact on cardiovascular outcome or disease progression. The more recent introduction of alpha glucosidase inhibitors and glitinides continued this focus on hyperglycaemia by inhibition of absorption and stimulation of insulin release respectively. Tighter blood sugar control, emphasized in current guidelines (Watkins, 2002), is often at the expense of side effects: hypoglycaemia with sulphonylureas or insulin is a specific concern. Disquiet over the safety of newer agents and the recent withdrawal of inhaled insulin have increased uncertainty over optimal treatment.

Type 2 diabetes is characterized by two specific defects: insulin resistance and impaired beta cell function. Both need to be present for type 2 diabetes to develop. On average beta cell function has declined by 50% at the time of diagnosis (UK Prospective Diabetes Survey, 1995) with inexorable further loss over 5–8 years regardless of treatment and dietary changes. The reasons for this loss of beta cell function are not understood but may result from both glucotoxicity and lipotoxicity.

By improving insulin sensitivity in muscle and liver, as well as modifying the metabolic abnormalities of adipose tissue, the thiazolidinediones (glitazones) offer a novel mechanism of reducing glucose levels, albeit at the expense of weight gain and exacerbation of heart failure. Their longer-term role has become more difficult to assess with the reported class effect of osteoporosis, and the alleged increased risk of myocardial infarction with rosiglitazone (Kazi, 2007).

Incretin hormones stimulate beta cell secretion and may also inhibit glucagon release from alpha cells. Exogenous subcutaneous administration of an incretin mimetic is now possible. Potentiation of endogenous incretins may also be achieved by oral inhibition of dipeptidyl peptidase-IV (DPP-IV), the enzyme that inactivates incretins. As well as having specific effects on the pancreas, these agents do not increase weight. Since DPP-IV inhibitors only potentiate physiological incretin release in response to a meal, they have a very low risk of hypoglycaemia. Preliminary reports also suggest that they may slow beta cell loss.

The incretin effect

A role for intestinal peptides was suggested in the 1960s after observing that an oral glucose load produced a greater insulin response than the equivalent load given intravenously (*Figure 1*). Labelled 'incretins', two predominant hormones, glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), were identified. These hormones are released following food ingestion and contribute between 25% and 60% of insulin secretion in healthy subjects. This response is reduced in patients with type 2 diabetes (Nauck et al, 1993).

Circulating levels of GLP-1, the more important of the incretin hormones, are reduced in diabetes but, importantly, there is preserved insulinotropic effect. Infusion of GLP-1 has been shown, in type 2 diabetic patients, to increase insulin secretion and lower glucagon levels. Furthermore GLP-1 infusions can increase beta cell sensitivity to an increase in glucose levels, with the glucose-lowering effect preserved in patients in whom sulphonylurea therapy has failed (*Table 1*, *Figure 1*).

Dr Hugh F McIntyre *is Consultant Cardiovascular Physician and*
Dr Paul Grant *is Specialist Registrar in Diabetes and Endocrinology in the Department of Medicine, Conquest Hospital, Hastings, East Sussex TN37 7RD*

Correspondence to: Dr HF McIntyre

Reduced glucagon secretion may be of particular benefit. In contrast to normal individuals, where glucagon secretion is suppressed by glucose ingestion, in type 2 diabetics glucagon concentrations are high with respect to insulin and glucose levels, which may promote hyperglycaemia. Underlying these observations are histological studies which suggest a parallel rise in alpha cell and fall in beta cell numbers in patients with diabetes. Animal studies indicate that GLP-1 administration may in part reverse these changes through increased regeneration and decreased beta cell apoptosis (Gedulin et al, 2005).

Incretin mimetics

GLP-1 is rapidly inactivated through cleavage by DPP-IV, and in studies requires continuous infusion. Drug development therefore focussed on incretin analogues and incretin receptor agonists (incretin mimetics). Saliva from the Gila monster, a desert lizard capable of extended periods of starvation, contains exendin, an incretin mimetic with about 50% homology with GLP-1 (Clark, 2006). Exendin (exenatide, Byetta, Eli Lilly & Amylin Pharmaceuticals, Indianapolis), available as a twice-daily subcutaneous injection, has been shown to reduce baseline HbA_{1c} (glycosylated haemoglobin) by 1.1% and fasting plasma glucose by 1.1 mmol for up to 2 years in type 2 diabetics (DeFronzo et al, 2005; Drucker, 2005). This improvement in glycaemic control is associated with reduction in body weight. Since they are large polypeptides both exenatide and liragutide (in phase III development) require subcutaneous or intravenous administrations. The clinical uptake of exenatide has been rapid, but recent reports of pancreatitis are a cause for concern (Food and Drug Administration, 2007). GLP-1 analogues have been described in more detail elsewhere (Scheen, 2007).

Figure 1. Insulin release following oral glucose load is greater than after isoglycaemic IV load in healthy controls (left panels). This response is diminished in patients with type 2 diabetes (right panels). *P≤0.05 vs respective value after oral load. Adapted from Nauck et al (1986).

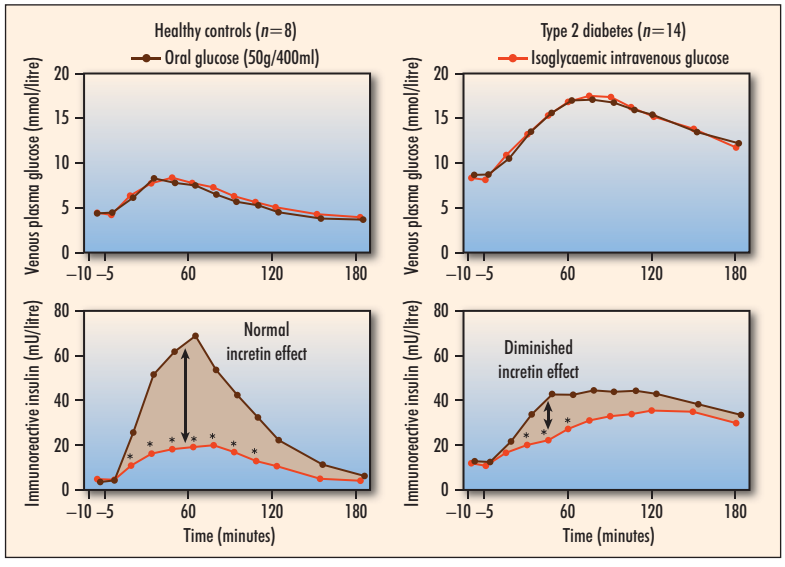

Table 1. Physiological actions of incretin hormones

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

Dipeptidylpeptidase-IV

DPP-IV is the main proteolytic enzyme responsible for the rapid (less than 2 minutes) inactivation of GLP-1 and GIP into metabolites that are devoid of insulin-releasing activity (Pratley and Salsali, 2007). The DPP-IV inhibitors that have reached late development are low molecular weight drugs with high oral bioavailability. They provide competitive, reversible inhibition of DPP-IV providing up to 90% inhibition of plasma DPP-IV activity during a 24-hour period. This leads to increased levels of endogenous GLP-1 and improvements in prandial insulin release, glucose control and HbA_{1c} (Vella et al, 2007). Improvements in islet cell survival and beta cell mass have also been shown in rodent models (Wajchenberg, 2007).

Collectively known as 'gliptins', sitagliptin (Januvia, Merck & Co., Whitehouse Station, NJ, USA) is currently the only DPP-IV inhibitor licensed for use in the UK. Vildagliptin (Galvus, Novartis, Basel, Switzerland) is awaiting approval and saxagliptin is in development. In contrast to insulin, sulphonylureas and glitazones, DPP-IV inhibitors do not cause weight gain.

Clinical evidence for DPP-IV inhibitors

The benefit of monotherapy with vildagliptin and sitagliptin was shown in two short-term double-blind trials in patients with moderate glycaemic control (HbA_{1c} 8.0%). In a safety and dose-finding study in 741 patients, sitagliptin reduced HbA_{1c} levels by 0.7% over 24 weeks, with minimal adverse drug reactions (Aschner et al, 2006). The incidence of hypoglycaemia was similar to placebo, with improvement in fasting and postprandial glycaemic control and measures of beta-cell function. Gastrointestinal side effects were slightly more common with sitagliptin. A similar reduction in HbA_{1c} was seen after monotherapy with vildagliptin for 12 weeks, and vildagliptin significantly reduced prandial glucagon levels.

Three European phase III clinical trials have shown similar benefit with addition of sitaglipitin to baseline metformin or pioglitazone therapy. On average the mean reduction in HbA_{1c} was 0.7% with greater reduction in

poorly controlled participants with baseline HbA_{1c} >9.5%. Gliptins also significantly reduced fasting plasma glucose as well as postprandial glucose, without any effect on weight.

Charbonnel et al (2006) investigated the addition of sitagliptin to baseline metformin in 701 patients aged 19–78 years with mild to moderate hyperglycaemia (mean HbA_{1c} 8.0%) receiving metformin (1500 mg/day). Following a run-in and stabilization phase patients were randomly assigned to receive placebo or sitagliptin 100 mg once-daily in a 1:2 ratio for 24 weeks. At week 24, sitagliptin treatment led to significant (P<0.001) reductions in HbA_{1c} (–0.65%), fasting plasma glucose and 2-hour post meal glucose compared to placebo. Indices of beta cell function also showed significant improvement. A greater proportion of patients achieved an HbA_{1c} <7% with sitagliptin (47.0%) than with placebo (18.3%). There was no increased risk of hypoglycaemia or gastrointestinal adverse experiences with sitagliptin compared with placebo.

Rosenstock et al (2006) compared sitagliptin or placebo in combination with pioglitazone. After a complex dietary and open-label pioglitazone dose titration/stabilization period, patients with an HbA_{1c} between 7% and 10% receiving pioglitazone (30 or 45 mg/day), received sitagliptin 100 mg once daily or placebo. After 24 weeks, the addition of sitagliptin to pioglitazone was associated with significant reductions in HbA_{1c} of –0.70%; P<0.001) and fasting plasma glucose (–17.7 mg/dl; P<0.001) compared with placebo. Mean HbA_{1c} values fell to 7.2% and 7.8% in the respective treatment groups, with 45.4% and 23.0% (P<0.001) reaching a target HbA_{1c} of <7.0% respectively. Significant reductions in fasting serum pro-insulin levels and the pro-insulin:insulin ratio were seen with sitagliptin treatment compared with placebo.

Clarification of the clinical role of gliptins is provided by Nauck et al (2007), who compared the addition of sitagliptin or sulphonylurea to patients inadequately controlled on metformin alone. After a metformin dose titration/stabilization period (≥1500 mg/day), 1172 patients were randomized to the addition of sitagliptin 100 mg once daily or glipizide 5 mg/day (up-titrated to a potential maximum 20 mg/day) and followed for 52 weeks. While both achieved an equivalent reduction in HbA_{1c}, there was a significant decrease (32 *vs* 5%, P<0.001) in the number and frequency of hypoglycaemic episodes in the patients on sitagliptin. In addition weight rose slightly with glipizide and fell with sitagliptin (at week 52: glipizide: +1.1 kg, sitagliptin: –1.5 kg, P<0.001).

Phase III studies of vildagliptin have found similar results. When compared to metformin monotherapy in 780 patients with a baseline HbA_{1c} of 8.7%, vildagliptin 100 mg daily provided similar reduction in HbA_{1c} over 12 months (to 7.56% and 7.4% for vildagliptin and metformin respectively, P<0.001). However, diarrhoea (6% *vs* 26%) and nausea (3% *vs* 10%) were far less common in the gliptin group (Schweizer et al, 2007).

In a further 296-patient phase III study comparing vildagliptin with placebo in patients requiring insulin therapy, vildagliptin 100 mg once per day plus insulin significantly reduced HbA_{1c} by 0.51% compared to a reduction of 0.24% by placebo plus insulin (P<0.001). Vildagliptin almost halved patients' insulin requirements compared to placebo (2.64 *vs* 4.97 IU) while avoiding hypoglycaemic episodes (0 *vs* 6) (Fonseca et al, 2007).

The combination of vildagliptin with pioglitazone has also recently been shown to afford comparable improvement in diabetic control to the addition of sitagliptin to pioglitazone (Rosenstock et al, 2007).

Together these trials demonstrate significant and reproducible glucose-lowering effects over the medium term using DPP-IV inhibitors. The hypothetical advantage of their 'physiological' mode of action is borne out by the reduced risk of hypoglycaemia compared with traditional oral hypoglycaemic agents. In addition stability of body weight, which may reflect endocrine mechanisms involved in the incretin response and satiety, also contrasts with traditional oral hypoglycaemic agents.

Sitagliptin (100 mg once per day) is currently indicated as add-on therapy when first-line treatment with either metformin or glitazone does not provide adequate glycaemic control. The role of gliptins as first-line therapy for those patients in whom side effects or contraindications preclude first-line use of metformin or glitazone requires further clarification.

Tolerability and safety

Clinical adverse reaction rates are low; nausea, a common early side effect of DPP-IV inhibitors, is generally mild and dissipates with time. Sitagliptin, an active compound with a plasma half-life of more than 10 hours, is actively excreted from the kidneys so renal function should be monitored initially, and use should be cautious where there is significant renal impairment. Vildagliptin metabolism is predominantly hepatic, with a plasma half-life of about 3 hours. Metabolites have possible biological activity. Other than a slight increase in digoxin levels (Nigam et al, 2007), few drug interactions have been reported to date.

One early concern has been that DPP-IV is found throughout the body, and functions as CD-26 – a T-cell activating antigen. This is a cell surface and circulating peptidase enzyme which is expressed in the gastrointestinal tract, pancreas, kidneys, thymus gland and elsewhere. The role of CD-26 in the normal immune system is uncertain, but its absence (in animal 'knockout' models) is not deleterious (Marguet et al, 2000). So far, treatment with gliptins has not been associated with any serious adverse outcomes. Formal, longer-term outcome studies are needed before safety and efficacy can be fully assessed.

Conclusions

By 2010 there will be three million people in the UK with diabetes. This number will continue to rise. Until recently, available treatments did not directly address the underlying pathophysiology and risked side effects, including hypoglycaemia.

Insulin resistance and decline in pancreatic cell function define type 2 diabetes. Glitazones improve insulin sensitivity and glycaemic control but uncertainty remains over the longer-term benefit. The incretin hormones enhance prandial insulin release and may improve pancreatic beta cell function. Potentiation of incretins is now possible through the oral administration of DPP-IV inhibitors, which have been shown to improve glycaemic control. Importantly their 'physiological' mode of action seems to reduce the risk of hypoglycaemia. These agents are also well tolerated and weight neutral.

DPP-IV inhibitors are potentially important therapies in diabetes, but join a market that is confused and wary of new agents. Their specific properties suggest that initial use might best be considered in those intolerant of conventional agents who wish to avoid insulin, and those who are overweight. In addition avoidance of hypoglycaemia is particularly important in older patients.

Safety and outcome data will be vital, but if longer-term studies substantiate the promise of improved beta cell function, for example by deferring the need for insulin, then we might start to be able to consider pancreatic 'maintenance' therapy. Perhaps not 'fixing' diabetes yet – but a step closer? Time will tell. **BJHM**

Conflict of interest: Dr McIntyre has been reimbursed for advisory roles, travel expenses and support for conference attendance by manufacturers of dipeptidyl peptidase-IV inhibitors. Dr Grant has no conflict of interest.

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KEY POINTS

- There remains a pressing need for safe, effective, well tolerated oral glucose-lowering agents.
- Incretin hormones promote physiological insulin release and may enhance beta cell function which is impaired in type 2 diabetes.
- Oral dipeptidyl peptidase-IV inhibitors potentiate the effect of endogenous incretin hormones.
- Dipeptidyl peptidase-IV inhibitors improve glycaemic control in type 2 diabetes, appear safe, are well tolerated and do not cause weight gain.

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