Review

Gliptins: a new class of oral hypoglycaemic agent

H. CHAHAL and T.A. CHOWDHURY

From the Department of Diabetes and Metabolism, The Royal London Hospital, London, UK

Summary

The epidemic of type 2 diabetes worldwide continues unabated. Despite a number of existing therapies, treatment goals are seldom fully achieved. While insulin resistance and beta cell failure remain important in the pathogenesis of the condition, the role of incretin hormones in glucose homeostasis has recently become clearer. Incretins have several glucoregulatory mechanisms, and a novel approach to the treatment of type 2 diabetes focuses on enhancing and prolonging the physiological actions of these hormones. Gliptins inhibit the enzyme dipeptidyl peptidase-IV (DPP-IV), which degrades incretin hormones. These drugs are a promising new class of oral hypoglycaemic medication, which appear to be weight-neutral and have few side-effects, although the published clinical studies are mainly regulatory licensing studies. As these drugs now are available for clinical use, we discuss the mechanism of action, efficacy and potential adverse effects of this new class of oral hypoglycaemic agent.

Introduction

Diabetes mellitus is a growing health problem. It currently affects 246 million people worldwide (5.9% of all adults), and is predicted to increase to 380 million adults within 20 years. In the UK, over 2.2 million people have the condition, of whom 90% have type 2 diabetes. Complications related to diabetes can lead to serious morbidity, and significantly reduced life expectancy. With the rise in incidence of type 2 diabetes over the next 20 years, the management of this chronic condition will present a serious clinical and financial burden to all health-care systems.

The pathophysiology of type 2 diabetes involves a complex interplay of genetic and environmental factors. The condition is characterized by peripheral insulin resistance (muscle, liver and adipocytes), and associated defects in insulin secretion due to decline in beta-cell function, and ultimately beta-cell failure (Figure 1). Insulin resistance is a phenomenon that appears to occur early, with seeds sown in childhood, while pancreatic beta-cell function declines over time, eventually leading to hyperglycaemia. Physiological mechanisms proposed for insulin resistance include an elevation in free fatty acids, decrease in adiponectin levels, involvement of inflammatory cytokines and defects in mitochondrial function. Decline in beta-cell function may be due to glucotoxicity, (glucose reversibly modifies the function of the beta-cell), lipotoxicity (increased circulating free fatty acids cause beta-cell damage), and the involvement of islet amyloid polypeptide (amylin). Many other pathogenic factors have been suggested for the development of type 2 diabetes, including peroxisome proliferator-activated receptor-gamma (PPARγ) activation and glucagon excess.

Current strategies for the treatment of type 2 diabetes have focused on reducing insulin resistance and increasing insulin secretion (Table 1). Biguanides (metformin) and sulphonylureas have
been the mainstay of therapy for diabetes for many years. More recently, thiazolidinediones have found an important role in augmenting the amelioration of insulin resistance, although there have been recent concerns over safety. Meglitinide analogues and alpha-glucosidase inhibitors have some role in treatment of diabetes, although their role is limited by cost and side-effects. Insulin therapy is frequently required in many people with long duration of type 2 diabetes, due to inexorable beta cell decline. Despite current therapeutic options, only 22% of diabetes patients in England achieve a glycated haemoglobin (HbA1c) <6.5%, with 42% having an HbA1c >7.5%. This may in part be due to the fact that traditional treatments for type 2 diabetes do not address the progressive decline in beta-cell function.

**Incretin hormones**

The role of the gastrointestinal tract in regulating the secretion of insulin is demonstrated by the observation that insulin secretion is substantially increased in response to oral glucose, compared to intravenous glucose administration. This difference is known as the *incretin effect* (Figure 2). These peptides are secreted from endocrine cells (L-cells) in the gastrointestinal tract, and are released in response to ingestion of food. The two main incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP),
with GLP-1 being responsible for most of the incretin effect on pancreatic beta-cell function. \textsuperscript{10}

GLP-1 regulates glucose homeostasis in the post-prandial period by a number of mechanisms, including stimulation of insulin synthesis, inhibition of glucagon secretion, delay in gastric emptying, and promotion of satiety.\textsuperscript{12} (Figure 3).

Following oral ingestion of nutrient, patients with type 2 diabetes have a decreased incretin effect, due to a reduction in the secretion of GLP-1, resulting in inappropriately low insulin secretion, inadequate for glucose homeostasis.\textsuperscript{13} GLP-1 administration is effective in people with type 2 diabetes, with an increase in insulin secretion and reduction of both fasting and post-prandial blood glucose.\textsuperscript{14} Administration of GLP-1 \emph{in vivo}, however, is problematic, as it is rapidly inactivated by the proteolytic enzyme dipeptidyl peptidase-IV (DPP-IV). DDP-IV cleaves the N-terminal amino acids of GLP-1,\textsuperscript{15} and is widely expressed in many tissues, including the capillary bed of the gut mucosa. Its close presence to GLP-1-secreting endocrine cells results in the rapid degradation of GLP-1 within minutes of release.\textsuperscript{13}

Two main therapeutic strategies have been developed to overcome this. The first involves the use of a long acting GLP-1 receptor agonist, resistant to the cleavage of DPP-IV. Exendin-4, or Exenatide (Lilly), is one such analogue that is licensed for use in patients with type 2 diabetes who have inadequate glucose control with metformin, sulphonylurea or both. It is administered as a twice-daily fixed-dose injection, and leads to a modest reduction in HbA\(_1c\) (0.8\%), and around 2.5 kg weight loss.\textsuperscript{16}

The second strategy is to use DPP-IV inhibitors (gliptins), which lead to inhibition of the degradation of GLP-1, thus enhancing the incretin effect.

\textbf{Figure 3.} Physiology of GLP-1 secretion and action. Reprinted with permission from Elsevier (Lancet 2006; 368: 1696–705) (reference 12).
Gliptins

Gliptins are a novel class of oral anti-diabetic agent that enhance and prolong the physiological actions of incretin hormones by competitively antagonizing the enzyme DPP-IV (Figure 4). Animal studies demonstrate the anti-diabetic properties of DPP-IV inhibitors, with a delay of progression from impaired glucose tolerance to type 2 diabetes, an improvement in glucose tolerance and insulin secretion, an improvement in beta-cell function and an increase in hepatic and peripheral insulin sensitivity.

A number of DDP-IV inhibitors are under investigation for the treatment of type 2 diabetes in humans. Vildagliptin (Novartis) and sitagliptin (Merck) are currently the only two gliptins with clinical trial data looking at their use as monotherapy and combination therapy with existing oral hypoglycaemics. These randomized, controlled, multicentre trials have shown a modest statistically significant reduction in HbA1c, when used as monotherapy or in combination.

Vildagliptin

Monotherapy

In a 12-week study, vildagliptin (at doses of 50 and 100 mg) significantly decreased HbA1c by 0.5–0.6% when given to patients who had not been treated with anti-diabetes medications for at least 12 weeks. A further 12-week study of vildagliptin, at a dose of 25 mg twice a day in drug-naive patients with type 2 diabetes, demonstrated a reduction in HbA1c of 0.6%, with a greater response of 1.2% occurring in those patients with an HbA1c >8%. A 24-week study in drug-naive patients, comparing monotherapy with vildagliptin 50 mg twice daily vs. rosiglitazone 8 mg daily showed a similar significant HbA1c reduction (1.1 vs. 1.3%). One 24-week trial in drug-naive patients given vildagliptin at doses of 50 mg, 50 mg twice a day and 100 mg showed significant reductions in HbA1c of 0.8%, 0.8% and 0.9%, respectively. At higher baseline HbA1c, there was a greater improvement in glycaemic control at the higher dose of vildagliptin 100 mg. Another 24-week trial in drug-naive patients treated with vildagliptin doses of 50 mg, 50 mg twice a day and 100 mg showed reductions in HbA1c of 0.5%, 0.7% and 0.9%, respectively.

Combination therapy

In a 52-week trial, vildagliptin 50 mg was given to patients already treated with metformin (1500–3000 mg daily), and resulted in a reduction in HbA1c at 12 weeks of 0.6%. A 24-week trial in patients inadequately controlled on metformin monotherapy showed that vildagliptin as an add-on therapy at a dose of 50 mg or 100 mg reduced HbA1c by 0.7% and 1.1%, respectively. In a 24-week trial of patients inadequately controlled by prior pioglitazone 45 mg monotherapy, vildagliptin was used as add-on therapy at doses of 50 mg and 100 mg, resulting in reductions in HbA1c of 0.8% and 1.0%, respectively. A more recent 24-week trial in drug-naive patients demonstrated that combination therapy with vildagliptin and pioglitazone provided better glycaemic control than either monotherapy component. A combination of vildagliptin 100 mg and pioglitazone 30 mg reduced HbA1c by 1.9%, compared to 1.1% with vildagliptin monotherapy and 1.4% with pioglitazone monotherapy.

Sitagliptin

Monotherapy

In a 12-week study in drug-naive patients, sitagliptin 50 mg reduced HbA1c by 0.8%. Over an 18-week study in drug-naive patients, sitagliptin, at doses of 100 and 200 mg, reduced HbA1c by 0.6% and 0.5%, respectively. Those patients with a baseline HbA1c >9% had the greatest reduction (1.2%). In a 24-week study, sitagliptin 100 and 200 mg produced reductions in HbA1c of 0.8% and 0.9%, respectively. Again, patients with a baseline HbA1c >9% had the greatest reduction (1.5%).

Combination therapy

In a 24-week trial in patients inadequately controlled on metformin therapy (>1500 mg/day), the addition

Figure 4. Gliptins targeting DPP-IV.
of sitagliptin 100 mg led to a HbA1c reduction of 0.7% compared to placebo.\textsuperscript{33} In another 24-week trial, sitagliptin 100 mg was given to patients inade-quately controlled on pioglitazone 30 and 45 mg. This resulted in HbA1c reductions of 0.7% and 0.9%, respectively.\textsuperscript{34} In a 52-week study in patients already treated with metformin (≥1500 mg/day) add-on therapy with sitagliptin 100 mg compared to glipizide 5 mg (up-titrated to a potential dose of 20 mg/day) provided similar HbA1c-lowering efficacy (0.7%).\textsuperscript{35}

In the US, sitagliptin has been licensed for use in monotherapy, or combination therapy with metformin or a PPAR\(\gamma\) agonist. The dose recommended orally is 100 mg, which should be adjusted in patients with moderate to severe renal disease.\textsuperscript{36} In the UK, a licence was obtained in April 2007 at a dose of 100 mg, but only as combination therapy with metformin or a PPAR\(\gamma\) agonist.\textsuperscript{37}

### Limitations of the clinical trials

While the studies described are randomized, multi-centre trials, they are pharmaceutically-sponsored, short-term studies, which describe proof of efficacy and lack of adverse effects over a very short time period. To date, only around 7000 patients have been exposed to gliptins. With recent concerns expressed over the cardiovascular effects of rosiglitazone,\textsuperscript{8} it is clear that further large, longer-term outcome studies will be required to ensure that these drugs are safe, effective and reduce complications in patients with type 2 diabetes.

### Adverse effects

Unlike incretin hormones, DPP-IV inhibitors do not act through specific targets on target tissues.\textsuperscript{38} DPP-IV is expressed in many tissues besides the gut mucosa, including T-cells, endothelium, liver, kidney and lung.\textsuperscript{12} A variety of chemokines, cytokines, growth factors and neuropeptides (pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal polypeptide, gastrin-releasing peptide, neuropeptide Y, growth-hormone-releasing hormone, GLP2, peptide YY, substance P), are inactivated by this enzyme.\textsuperscript{13} Thus given the wide spread substrates of DPP-IV and the prolongation of GLP-1 activity, DPP-IV inhibitors could have adverse effects in many systems. However, the small number of clinical studies have so far reported no significant adverse effects. In general, gliptins appear to be safe and well tolerated, with few reported side-effects, and the overall incidence of side-effects being similar to placebo. With vildagliptin, the most common side-effects were cold/flu-like symptoms, headache and dizziness. With sitagliptin, the most common side-effects were stuffy or runny nose, sore throats, headache, diarrhoea, upper respiratory infection, joint pains and urinary tract infection (differences ranging from 0.1–1.5% vs. placebo). In these trials, the overall incidence of hypoglycaemia has been similar to placebo and the gliptins appear to be weight-neutral, although in one study sitagliptin led to a 1.5 kg loss in weight.\textsuperscript{35} However, given the potential widespread targets for DPP-IV inhibitors, the full metabolic effects may not be apparent in these limited studies.

Although DPP-IV inhibitors and long-acting GLP-1 agonists both prolong the action of GLP-1, they have important differences with regards to weight loss and gastrointestinal side-effects. Compared to GLP-1 agonists, DPP-IV inhibitors are weight-neutral and have fewer gastrointestinal side-effects. This may be explained by the dose-dependent action on GLP-1 receptors, with DPP-IV inhibitors only causing a modest stabilization of post-prandial GLP-1 levels, resulting in minimal weight loss, as compared to more chronically elevated GLP-1 levels with GLP-1 agonists, resulting in delayed gastric emptying.\textsuperscript{12}

### The role of gliptins in the treatment of type 2 diabetes

While the improvement in glycaemic control with gliptins is moderate and no more effective than with metformin, sulphonylurea or thiazolidinedione treatment, they are potentially an attractive therapeutic option in the treatment of type 2 diabetes. They appear to be well tolerated, have a low risk of hypoglycaemia, do not cause weight gain and can be given orally once a day. These features are in contrast to the common side-effects of existing oral hypoglycaemic medications. While they may achieve a monotherapy licence, it would not be appropriate to use these drugs first line, due to their cost, and lack of long-term safety data. In obese patients, however, a case could be argued for gliptins to be used second line to metformin or third line to glitazones, especially as they are weight-neutral. Raised levels of GLP-1 may have a role in beta-cell growth and proliferation, hence it is important to investigate the potential role of gliptins in preventing progression of diabetes to the beta-cell failure. The role of gliptins in prevention of progression of impaired glucose tolerance also needs further study.
Conclusions

Diabetes is a long-term condition leading to macrovascular and microvascular complications, resulting in significant morbidity and premature mortality. The pathogenesis of type 2 diabetes has traditionally been thought to be related to insulin resistance and beta-cell failure. Newer insights, however, suggest that the pathogenesis of type 2 diabetes is much more complex, with the role of incretin hormones having been recently described. Enhancement of the incretin effect is now a potential therapeutic target in type 2 diabetes, using GLP-1 analogues and DPP-IV inhibitors.

Gliptins are a new class of oral anti-diabetic medication that prolong the physiological actions of GLP-1. Short-term clinical trials show that gliptins cause a modest reduction in glycated haemoglobin when used as monotherapy or combination therapy, of around 0.7–1%. They appear to be more potent when baseline glycated haemoglobin is higher. They appear to be well-tolerated, and are taken orally once daily. They may be useful in treating obese patients with type 2 diabetes, in combination with metformin, or a glitazone, or both.

The recent safety concerns over glitazones should remind all physicians using new drugs for any chronic disease that long-term pharmacovigilance is necessary, and long-term outcome studies are required to evaluate the effects of cardiovascular mortality and morbidity.

References


