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Hyperglycaemia in type 2 diabetes: Newer blood glucose lowering therapies

Neil Munro

Learning objectives

After reading this article, the participant should be able to:

1. Explain the incretin effect and how it has been exploited therapeutically for the treatment of type 2 diabetes.
2. Outline the indications and contraindications of exenatide, sitagliptin and vildagliptin.
3. Describe the key trial data underlining these newer blood glucose lowering agents.

Key words

- Exenatide
- Sitagliptin
- Vildagliptin

Established classes of glucose lowering agents, such as sulphonylureas, thiazolidinediones and insulin, effectively reduce blood glucose levels in people with type 2 diabetes. Their mode of action can result in hypoglycaemia, weight gain or both. Improved understanding of the "incretin" effect has enabled development of glucose lowering therapies that overcome some of the unwanted effects of earlier oral agents. Glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are associated with weight loss, or weight neutrality, and are less likely to cause hypoglycaemia than many glucose lowering therapies currently used in clinical practice due to their glucose-dependent mode of action. While these agents have been licensed for clinical use recently, there is currently a paucity of long-term data on safety and durability of their glucose-lowering effect.

Several new drugs designed to reduce hyperglycaemia in type 2 diabetes have been introduced into clinical practice in recent years. Established classes of oral blood glucose lowering agents, including biguanides, sulphonylureas, meglitinides, alpha-glucosidase inhibitors and thiazolidinediones (TZDs), as well as insulin, address hyperglycaemia in people with type 2 diabetes through a variety of mechanisms. While these agents compensate, in varying ways, for the diminished insulin secretion and enhanced insulin resistance that typify type 2 diabetes, their efficacy, to differing extents, is limited by hypoglycaemia, weight gain or both. In addition, each class of existing therapies has its own recognised contraindications, side-effects and interactions with other agents.

Improved understanding of pathophysiological processes underlying type 2 diabetes has enabled the development of glucose-lowering agents with new modes of action. The advent of glucagon-like peptide-1 (GLP-1) receptor agonists and

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dipeptidyl peptidase-4 (DPP-4) inhibitors are examples of such developments (Munro et al, 2007; Munro and Levy, 2007). These agents are distinguished from many existing therapies by their glucose-dependent mode of action. They offer the possibility of glucose control with weight loss, or at least weight neutrality, and a diminished risk of significant hypoglycaemia.

This module describes the development path and licensing trials for the newer blood glucose lowering agents, with an emphasis on the agents currently available to prescribers in the UK. Post-marketing trial evidence is largely unavailable for these agents, although several multicentre trials are in their preliminary phases.

In addition, the module covers key mechanisms currently being explored that may result, over the next 10 years, in the emergence of therapies with novel modes of action, further expanding the palette of agents available for clinical use.

The incretin system

Incretin hormones are peptides released from the intestinal tract in response to mixed meals. They contribute to glucose homeostasis by promoting glucose-dependent insulin secretion. The incretin effect is observed experimentally when insulin responses to oral and intravenous glucose loads are compared. An enhanced response is seen with oral, as opposed to parenteral glucose.

The role of an incretin mechanism in glucose homeostasis was proposed as long ago as the 1930s (La Barre, 1932). It was not until the 1960s, however, that researchers demonstrated an increased stimulation of insulin secretion when glucose is given orally rather than intravenously at equivalent doses (Elrick et al, 1964; Perley and Kipnis, 1967). Results indicated the presence of gastrointestinal-hormone mediated action leading to enhanced postprandial insulin secretion in response to oral glucose loading. Eisentraut and Unger called this "intestinal secretion of insulin" the "incretin" effect (Creutzfeldt and Ebert, 1985).

Two hormones secreted from the gastrointestinal tract account for >50% of the incretin effect of a mixed meal. They rapidly stimulate insulin release in the presence of hyperglycaemia. These hormones are GLP-1, comprising 30 amino acids, and glucose-dependent insulinotropic polypeptide (GIP), comprising 42 amino acids (McIntyre et al, 1964; Nauck et al, 1986). GIP is derived from the K cells located in the jejunum and is secreted more readily in response to dietary fat than to glucose (Levy, 2006). In contrast, GLP-1 is secreted by the L cells in the ileum, predominantly in the presence of glucose.

The secretion of these hormones occurs in association with neural signalling arising from food stimulus. These mechanisms induce insulin secretion through direct activation of G-protein coupled receptors expressed on pancreatic beta-cells (Vilsboll and Holst, 2004). In people with type 2 diabetes the beta-cell response to GIP is largely lost, but GLP-1 receptor sensitivity remains (Munro and Feher, 2008). The reasons for reduced GIP responsiveness remain unclear but may be associated with reduced GIP receptor expression in people with significant insulin resistance (Rudovich et al, 2005). Drug developments have therefore focused on the role of GLP-1 in glucose homeostasis.

Native GLP-1

Insulin secretion in response to glucose metabolism is triggered by beta-cell membrane depolarisation. This raises intracellular calcium concentrations, which, in conjunction with calmodulin, causes insulin granules to fuse with the cell membrane, releasing their contents to the extracellular medium.

Cellular signalling mechanisms provide a rationale for incretin hormone effects. When GLP-1 binds to beta-cell surface receptors, cyclic adenosine monophosphate-dependent protein kinase activation results. This potentiates the insulin secretory pathway at many points, enhancing secretion. However, as GLP-1 cannot trigger insulin release by itself, its insulinotropic effect is dependent on ambient glucose. At glucose levels close to the threshold for the triggering of insulin secretion, GLP-1 has little effect (Triplitt et al, 2006).

In addition to its glucose-dependent action on insulin secretion, GLP-1 has been shown to suppress glucagon secretion, delay gastric emptying, and induce satiety and a sense of fullness, with a resultant reduction in food

Page points

1. Incretin hormones are peptides released from the intestinal tract in response to mixed meals that contribute to glucose homeostasis by promoting glucose-dependent insulin secretion.
2. The incretin effect is observed experimentally when insulin responses to oral and intravenous glucose loads are compared. An enhanced response is seen with oral, as opposed to parenteral glucose.
3. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) account for the majority of the incretin effect of a mixed meal.
4. In people with type 2 diabetes the beta-cell response to GIP is largely lost, but GLP-1 receptor sensitivity remains.

CPD module

Page points

1. In addition to its glucose-dependent action on insulin secretion, glucagon-like peptide-1 (GLP-1) has been shown to suppress glucagon secretion, delay gastric emptying, and induce satiety and a sense of fullness, with a resultant reduction in food intake.
2. Exenatide exhibits several of the antihyperglycaemic properties of GLP-1, and has been shown to bind to and activate the human GLP-1 receptor.

intake (Levy, 2006). Elevated glucagon levels are found in people with type 2 diabetes and contribute to background and postprandial hyperglycaemia. By direct action on islet alpha-cells, GLP-1 reduces excess glucagon secretion without impacting on its protective effect during hypoglycaemia.

The combination of delayed gastric emptying and a central nervous system effect on satiety, via GLP-1 mediated activation of receptors in the hypothalamus and area postrema, offers the potential for weight reduction (Orskov et al, 1996). In rodents suppression of apoptosis and proliferation of beta-cells has been demonstrated (Drucker, 2003). These properties are summarised in *Box 1*.

Exploiting the therapeutic potential of the incretin system

The effects of GLP-1 outlined above would clearly be useful in a blood glucose lowering therapy for type 2 diabetes. The potential for achieving glucose homeostasis with minimal risk of iatrogenic hypoglycaemia is clearly desirable, as is the possibility of weight loss. As the site of action of GLP-1 is distinct from those of other insulin secretagogues, it has the advantage of providing an additive, rather than competitive, effect (Zander et al, 2002). Furthermore, were the beta-cell protective properties observed in animal studies to be demonstrated in humans also, a treatment able to prevent the beta-cell decline that typifies type 2 diabetes would be represent a significant milestone.

Native GLP-1 is, however, not easily exploitable as a therapy for type 2 diabetes. Owing to its rapid degradation by DPP-4, the agent has a short half-life, and a native GLP-1 therapy would require continuous parenteral infusion. As such, efforts to therapeutically exploit the incretin system have focused on two drug classes – long-acting GLP-1 receptor agonists (also known as incretin "mimetics") and DPP-4 inhibitors.

Box 1. Modes of action of glucagon-like peptide-1 (Drucker et al, 2001; 2003).

- Stimulates glucose-dependent insulin secretion.
- Suppresses glucagon secretion.
- Slows gastric emptying.
- Reduces food intake.
- Improves insulin sensitivity.
- Increases in beta-cell mass and beta-cell efficiency have been demonstrated in animal studies.

Box 2. Exenatide: key facts and practical considerations.

- Administered subcutaneously at a dose of 5 µg or 10 µg twice-daily.
- Reduces HbA_{1c} by approximately 0.5–1%.
- Associated with weight loss.
- May be used in combination with metformin, a sulphonylurea, or both.
- Hypoglycaemia has been observed when exenatide is used in combination with a sulphonylurea. It is therefore recommended that a reduction in the dose of sulphonylurea be considered.
- Most common side-effect is mild to moderate nausea.
- Included in NICE's 2008 guideline on the management of type 2 diabetes (*Box 5*).
- Pancreatitis has been reported as an adverse effect.

GLP-1 receptor agonists

GLP-1 receptor agonists mimic the action of native GLP-1, but are resistant to degradation by DPP-4.

Exenatide

History

The first GLP-1 receptor agonist to become commercially available is exenatide (*Box 2*). Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster, a poisonous Mexican lizard, which has a 50% homology with human GLP-1. Exenatide has been licensed in the USA for the treatment of type 2 diabetes since 2005. In the UK the agent has been commercially available since 2007.

Mode of action

Exenatide exhibits several of the antihyperglycaemic properties of GLP-1, and has been shown to bind to and activate the human GLP-1 receptor (Electronic Medicines Compendium, 2009). In common with GLP-1, the agent stimulates glucose-dependent insulin secretion, suppresses glucagon secretion and delays gastric emptying.

Indications and licence

Exenatide is indicated for the treatment of type 2 diabetes in combination with metformin,

sulphonylureas, or both in people who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

The agent is administered via twice-daily subcutaneous injection. To reduce early side-effects such as nausea, the initial dose is 5 µg twice-daily. This can be increased to 10 µg after 1 month to further improve glycaemic control. Injections should be administered within the 60 minutes before morning and evening meals (or the two main meals of the day, providing that they are approximately >6 hours apart).

When used in combination with a sulphonylurea, it is recommended that a reduction in the dose of sulphonylurea be considered as a means of minimising the risk of hypoglycaemia (Electronic Medicines Compendium, 2009).

Key evidence: Placebo-controlled trials examining combination with oral agents

Phase III trials involving 1600 people with type 2 diabetes treated over a minimum of 6 months evaluated exenatide as additional therapy in those who had not achieved satisfactory glycaemic control with maximum doses of metformin, sulphonylureas or a combination of both agents (Buse et al, 2004; DeFronzo et al, 2005; Kendall et al, 2005). In all studies, exenatide 10 µg twice-daily reduced HbA_{1c} by about 1% when compared with placebo over 30 weeks. When exenatide 10 µg twice-daily was added to metformin there was a 2.8 kg weight loss. This weight loss did not appear to plateau at the end of the study period (DeFronzo et al, 2005).

In a shorter 16-week study comparing exenatide with placebo when taken in combination with a TZD with or without metformin the agent was associated with a reduction of HbA_{1c} approaching 1% (Zinman et al, 2007). Exenatide is not currently licensed for use in combination with TZDs.

Key evidence: Comparison with insulin

In a 26-week study, 549 people with type 2 diabetes and an HbA_{1c} level of 7–10% on metformin and sulphonylurea were randomised to receive either exenatide or insulin glargine (titrated using a forced protocol aiming for a morning blood glucose level of 100 mg/dL [5.6 mmol/L]) (Heine et al, 2005). The percentages of patients achieving an HbA_{1c} level of ≤7% (48% vs. 46%, respectively) and ≤6.5% (32% vs. 25%) were not significantly different. Weight loss in the exenatide arm was 2.3 kg, while weight gain in the insulin glargine recipients was 1.8 kg (P<0.001).

The therapeutic effects of insulin glargine and exenatide when added to either metformin or sulphonylurea monotherapy were compared in a 32-week crossover study (Barnett et al, 2007). On an intention-to-treat basis, 138 people with a mean BMI of 31 kg/m^2, an HbA_{1c} level of 9% and 7 years' duration of diabetes were randomised to treatment with exenatide or insulin glargine plus either sulphonylurea (45%) or metformin (55%) therapy. After 16 weeks, participants' treatment regimens were crossed over.

Similar percentages of trial participants reached an HbA_{1c} target of ≤7% – 38% with exenatide and 40% with insulin glargine – with 22% and 14% achieving an HbA_{1c} level ≤6.5%, respectively. Body weight changes observed in the first 16 weeks of the trials were effectively reversed when the treatments were crossed over (Barnett et al, 2007).

A comparison of exenatide and premixed insulin aspart exhibited similar results, with equivalence in HbA_{1c} reductions (1.04% vs. 0.89%, respectively) and a divergence in weight effects (Nauck et al, 2007a). A higher percentage of people in the exenatide arm compared with the insulin aspart arm achieved an HbA_{1c} level of ≤7% (32% vs. 24%, respectively).

Contraindications and side-effects

The most common side-effect in studies of exenatide in combination with other oral blood glucose lowering agents was mild to moderate nausea, with a prevalence of 36–39% (with 5 µg twice-daily) and 45–50% (with 10 µg twice-daily) (Riddle et al, 2006). However, this generally dissipated in the early weeks of therapy (Riddle et al, 2006). Overall, in the studies by Buse et al (2004), DeFronzo et al (2005) and Kendall et al (2005), 4% of exenatide recipients withdrew from the studies due to nausea.

There were reports of hypoglycaemia when exenatide was added to sulphonylurea but not

Page points

1. Exenatide is indicated for the treatment of type 2 diabetes in combination with metformin, sulphonylureas, or both in people who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.
2. The agent is administered via twice-daily subcutaneous injection. To reduce early side-effects such as nausea, the initial dose is 5 µg twice-daily. This can be increased to 10 µg after 1 month to further improve glycaemic control.
3. The most common side-effect in studies of exenatide in combination with other oral blood glucose lowering agents was mild to moderate nausea.

CPD module

Page points

1. Pancreatitis has been reported as an adverse effect of exenatide. Continuing advice is that if pancreatitis is suspected, treatment with exenatide should be suspended immediately; if pancreatitis is diagnosed, exenatide should be permanently discontinued.
2. Liraglutide is a once-daily GLP-1 receptor agonist that is currently awaiting licensing approval for use in clinical practice.
3. The LEAD (Liraglutide Effect and Action in Diabetes) study programme has examined its use in combination with sulphonylureas, metformin, thiazolidinediones and insulin.

to metformin. Adverse effects were related to dose, and slow titration reduced their incidence (Fineman et al, 2004).

Due to the increase in hypoglycaemia risk when exenatide is taken with a sulphonylurea, Group 2 (larger goods vehicle or passenger carrying vehicle) driving license holders treated with these agents in combination are required to inform the Driver and Vehicle Licensing Agency (DVLA, 2008).

In insulin comparator studies safety and tolerability were closely studied. Overall hypoglycaemia rates in the head-to-head comparison of exenatide and insulin glargine were low (7.3 vs. 6.3 events/year, respectively) (Heine et al, 2005). In the exenatide-treated people, this was thought to be attributable to concomitant sulphonylurea therapy. Low rates of hypoglycaemia were also observed in the comparison of exenatide and premixed insulin (daytime: 4.1 vs. 4.4 events/patient-year; nocturnal: 0.6 vs. 1.1 events/patient-year). One-third of people treated with exenatide experienced nausea; however, this resulted in a low drop out rate of 3.5%.

People with type 2 diabetes have a three-fold greater risk of developing pancreatitis compared with those without diabetes (Noel et al, 2009). In addition, those who are obese have a several-fold increased risk of developing severe complications of pancreatitis relative to non-obese people (Suazo-Barahona et al, 1998). Pancreatitis has been reported as an adverse effect of exenatide. As of March 2009, there have been approximately 800 000 patient-years of experience worldwide with the drug since it was licensed; in the period up to September 2008, there were 396 case reports of pancreatitis in people taking the agent (Medicines and Healthcare products Regulatory Agency [MHRA], 2009). According the MHRA (2009), nine reports of necrotising or haemorrhagic pancreatitis, two of which were fatal, have been received worldwide. Continuing advice is that if pancreatitis is suspected, treatment with exenatide should be suspended immediately; if pancreatitis is diagnosed, exenatide should be permanently discontinued (MHRA, 2009). There are no markers that determine whether pancreatitis associated with exenatide will be complicated by the haemorrhagic or necrotising forms.

Exenatide is not recommended for use in those with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min) (MHRA, 2009).

GLP-1 receptor agonists: Future developments

Studies examining the impact of prolonged action of GLP-1 receptor agonists are currently under way. Additional research has focused on the development of GLP-1 receptor agonists based on modification of the amino acid sequence of human GLP-1 to increase resistance to enzymatic degradation by DPP-4.

While exenatide is administered twice daily, other GLP-1 receptor agonist preparations administered once-daily or once-weekly are being studied in an effort to improve adherence and acceptability. Furthermore, fortnightly and monthly injectable, as well as inhaled, GLP-1 agents are being investigated. Examples of agents in development are albiglutide (Matthews et al, 2008), liraglutide, exenatide once-weekly and taspoglutide.

Liraglutide

Liraglutide is a once-daily GLP-1 receptor agonist that is currently awaiting licensing approval for use in clinical practice. The agent is based on the human GLP-1 sequence linked to a fatty acid (Juhl et al, 2002). It binds to interstitial albumin at the injection site and is slowly absorbed. The albumin complex delays absorption and is resistant to DPP-4 degradation, having a half-life of 12.6 hours (Agerso et al, 2002).

The LEAD (Liraglutide Effect and Action in Diabetes) study programme has examined its use in combination with sulphonylureas, metformin, TZDs and insulin. The LEAD studies included around 4000 people with type 2 diabetes; five randomised, controlled, double-blind studies were initially conducted in more than 40 countries.

LEAD-1 (Marre et al, 2009) and LEAD-2 (Nauck et al, 2009) investigated the effect of different doses of liraglutide when combined with a single oral antidiabetes drug: glimepiride and metformin, respectively.

LEAD-3 compared liraglutide with glimepiride when used as monotherapy (Garber et al, 2009), while LEAD-4 investigated the effect of different doses of liraglutide in combination with metformin and rosiglitazone (Zinman et al, 2009). LEAD-5 compared liraglutide with insulin glargine when used as add-on therapy in people inadequately controlled with metformin and glimepiride (Russell-Jones et al, 2008).

The most common adverse events in the trials were gastrointestinal in nature (i.e. nausea, diarrhoea and vomiting), and were mostly mild and transient. The rate of minor hypoglycaemia was low, at ≤0.5 events/patient-year. As with exenatide there were occasional reports of pancreatitis.

Exenatide once weekly

A once-weekly preparation of exenatide (exenatide QW) is currently in an advanced stage of development (Drucker et al, 2008). In a safety trial, exenatide QW lowered HbA_{1c} levels by 1.9% over 30 weeks, compared with a 1.5% reduction for exenatide twice-daily over the same period (P=0.0023) (Drucker et al, 2008). A similar degree of weight loss was noted in both arms.

DPP-4 inhibitors (gliptins)

Mode of action

DPP-4 inhibitors are oral agents that block DPP-4-mediated inactivation of GLP-1. This results in prolongation of endogenous GLP-1 activity, with higher fasting and postprandial plasma levels being achieved in vivo (Idris and Donnelly, 2007). This, in turn, increases insulin secretion, reduces the proinsulin-to-insulin ratio, inhibits glucagon secretion and reduces postprandial hyperlipidaemia. In contrast to GLP-1 receptor agonists, DPP-4 inhibitors appear to have a limited effect on weight and gastric emptying.

In addition to their impact on GLP-1 and GIP action, these agents may potentially affect other peptides, including peptide YY, neuropeptide Y, growth hormone-releasing hormone and vasoactive intestinal polypeptide, which are involved in regulatory systems (Deacon, 2004). It is further recognised that DPP-4 is important in T-cell activation. Long-term data on the use of DPP-4 inhibitors remains limited.

There have been over 100 patent applications for DPP-4 inhibitors to be used either as a monotherapy or in other drug combinations for the treatment of type 2 diabetes, metabolic syndrome, osteoporosis and arthritis (Chyan and Chuang, 2007). Sitagliptin and vildagliptin are commercially available in the UK with additional agents expected in the near future.

Sitagliptin

History

Sitagliptin is a potent and highly selective inhibitor of DPP-4, and was the first DPP-4 inhibitor to become commercially available (*Box 3*). It was licensed for use in the USA in 2006, with its UK license following in 2007.

Indications and licence

Sitagliptin is indicated for improving glycaemic control in combination with metformin, a sulphonylurea, or both metformin and a sulphonylurea, when diet and exercise plus maximally tolerated doses of these agents do not provide adequate glycaemic control. It is also indicated for dual therapy with a TZD when glycaemic control is suboptimal with diet and exercise and the TZD alone.

The dose of sitagliptin is 100 mg once daily. When sitagliptin is used with a sulphonylurea, a reduction in the dose of sulphonylurea may be considered to minimise the risk of hypoglycaemia (Electronic Medicines Compendium, 2008b). Sitagliptin should not be used in people with moderate to severe renal insufficiency (creatinine clearance <50 mL/min) due to a lack of data.

Page points

1. Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral agents that block DPP-4-mediated inactivation of glucagon-like peptide-1 (GLP-1).
2. This results in prolongation of endogenous GLP-1 activity, which in turn increases insulin secretion and reduces the proinsulin-to-insulin ratio, inhibits glucagon secretion and reduces postprandial hyperlipidaemia.
3. In contrast to GLP-1 receptor agonists, DPP-4 inhibitors appear to have a limited effect on weight and gastric emptying.

Box 3. Sitagliptin: key facts and practical considerations.

- Administered orally at a dose of 100 mg daily.
- Reduces HbA_{1c} by approximately 0.5–0.8%.
- Generally regarded as weight neutral.
- May be used in combination with metformin, a sulphonylurea, or both. May also be used in combination with a thiazolidinedione.
- The rate of hypoglycaemia has been observed to increase relative to placebo when sitagliptin is used in combination with a sulphonylurea. It is therefore recommended that a reduction in the dose of sulphonylurea be considered.
- Should not be used in people with moderate to severe renal insufficiency.

CPD module

Page points

1. In a number of studies, sitagliptin has been shown to improve levels of HbA_{1c}, fasting glucose and beta-cell function when compared with placebo.
2. Sitagliptin has also been investigated in combination therapy studies.
3. Vildagliptin is a competitive and reversible inhibitor of DPP-4 that became commercially available for use in the UK in 2008.

Key evidence: Placebo-controlled trials

In a number of studies, sitagliptin has been shown to improve levels of HbA_{1c}, fasting glucose and beta-cell function when compared with placebo. Aschner et al (2006) conducted a monotherapy study in which 741 patients were randomised to placebo, sitagliptin 100 mg daily or 200 mg daily over a 24-week period. HbA_{1c} reductions of 0.61% and 0.76% were recorded for the 100 mg and 200 mg groups, respectively, while HbA_{1c} increased by 0.18% in the placebo group. Additionally, fasting plasma glucose levels were reduced compared with placebo. Homeostasis model of assessment of beta-cell function (HOMA-B) showed an increase of 13% and a reduction in the proinsulin-to-insulin ratio, suggesting an improvement in beta-cell function with sitagliptin (Aschner et al, 2006). These findings were corroborated in another monotherapy study by Raz et al (2006). Sitagliptin is not currently licensed for use as a monotherapy.

Sitagliptin has also been investigated in combination therapy studies. Charbonnel et al (2006) randomised 701 people with type 2 diabetes and suboptimal glycaemic control (HbA_{1c} ≥7 and ≤10%) with metformin alone to receive either placebo or sitagliptin 100 mg for 24 weeks. Sitagliptin was associated with a statistically significant placebo-subtracted reduction in HbA_{1c} levels of 0.65%, and improvements in fasting and postprandial glucose levels. The proportion of participants achieving an HbA_{1c} level of <7% was also significantly greater in those assigned to sitagliptin than those receiving placebo (47.0% vs. 18.3%, respectively; $P<0.001$). Significant improvements with sitagliptin were also noted for indexes of insulin secretion and beta-cell function. No significant differences were noted between the groups in terms of safety, including the risk of hypoglycaemia. Finally, changes in body weight were not significantly different.

Additional placebo-controlled studies have examined the use of the agent in combination with sulphonylurea, sulphonylurea and metformin (Hermansen et al, 2007), and a TZD (Rosenstock et al, 2006). In both studies, sitagliptin was associated with reductions in HbA_{1c} and fasting glucose levels. There were modest increases in rates of hypoglycaemia with sitagliptin compared with placebo when the agent was added to sulphonylurea therapy, but not a TZD.

Key evidence: Comparator trials

Nauck et al (2007b) randomised 1172 people with type 2 diabetes and inadequate glycaemic control with metformin monotherapy to the addition of sitagliptin 100 mg once-daily or glipizide for 52 weeks. Similar reductions in HbA_{1c} were achieved by participants in both arms. Rates of hypoglycaemia were lower in the group assigned sitagliptin than in the group receiving glipizide (5% vs. 32%; $P<0.001$).

Scott et al (2008) examined the relative effects of placebo, sitagliptin and rosiglitazone when added to ongoing metformin monotherapy. Similar reductions in HbA_{1c} were observed in the active treatment arms; body weight increased in those assigned to rosiglitazone and decreased in those taking sitagliptin. The between treatment group difference in body weight change was statistically significant.

Further trials

Study data considering treatment with sitagliptin in children with type 2 diabetes aged 11–16 years, as well as treatment in combination with insulin in adults, are awaited.

Vildagliptin

History

Vildagliptin is a competitive and reversible inhibitor of DPP-4 that became commercially available for use in the UK in 2008 (*Box 4*). It is not currently licensed for use in the USA.

Indication and licence

Vildagliptin is currently licensed for the treatment of type 2 diabetes as dual oral therapy in combination with metformin, a sulphonylurea or a TZD. The recommended daily dose is 50 mg twice-daily when used with metformin or a TZD; 50 mg daily is the recommended dose when used with a sulphonylurea. There is also a fixed-dose combination of vildagliptin and metformin.

Prescribers are advised to monitor liver function at 3-month intervals during the first year of treatment with vildagliptin and periodically thereafter (Electronic Medicines Compendium, 2008a). Transient liver enzyme rises were noted during clinical trials with dosages higher than are available for clinical use.

Key evidence: Placebo-controlled trials

Bosi et al (2007) conducted a 24-week double-blind trial to evaluate the safety and efficacy of vildagliptin 50 mg daily and 100 mg daily compared with placebo, when added to metformin monotherapy in people with suboptimal glycaemic control. Placebo-subtracted reductions in HbA_{1c} of –0.7% and –1.1% were observed with vildagliptin 50 mg and 100 mg, respectively ($P<0.001$ for both). Improvements in levels of fasting plasma glucose and measures of beta-cell function were also noted.

In a 6-week insulin clamp study comparing vildagliptin with placebo, the gliptin was associated with an improvement in islet function and glucose metabolism in peripheral tissues (Azuma et al, 2008).

Fonseca et al (2007) compared the addition of vildagliptin 50 mg twice-daily or placebo to insulin therapy in inadequately controlled people with type 2 diabetes (HbA_{1c} 7.5–11%). A significant difference in the magnitude of HbA_{1c} reduction was observed between the groups (vildagliptin: –0.5%, placebo: –0.2%; $P=0.01$). In addition, no difference in insulin dosages were noted and fewer and less severe hypoglycaemic episodes were recorded in the vildagliptin treated group. Vildagliptin is not currently licensed for use with insulin.

Garber et al (2008) compared the addition of vildagliptin (at doses of 50 mg once- or twice-daily) and placebo to sulphonylurea monotherapy. An improvement in glycaemic control was noted in those assigned vildagliptin. Rates of hypoglycaemia were low but slightly higher in the group receiving 50 mg twice-daily.

Key evidence: Comparator trials

In a 1-year study comparing vildagliptin 50 mg twice-daily with metformin 1 g twice-daily in drug-naïve people with type 2 diabetes and baseline HbA_{1c} levels of 8.7%, the mean changes from baseline to endpoint HbA_{1c} were –1% and –1.4%, respectively. While non-inferiority of vildagliptin compared to metformin was not confirmed, the DPP-4 inhibitor did result in early and sustained improvements in glycaemic control (Schweizer et al, 2007). Gastrointestinal side-effects were less frequent than with metformin, and there was no change in weight and a low rate of hypoglycaemia with vildagliptin. Vildagliptin is not currently licensed for use as a monotherapy.

A further study compared vildagliptin 50 mg twice-daily with rosiglitazone 8 mg daily in drug-naïve people with type 2 diabetes. The mean change in HbA_{1c} for those on vildagliptin from baseline to endpoint was –1.1%, which satisfied the non-inferiority criterion of a ≤0.4% difference between treatments. Weight gain of 1.6 kg was observed over the 24-week study period in those treated with rosiglitazone, while those assigned vildagliptin did experience a change in body weight (Rosenstock et al, 2007).

Box 4. Vildagliptin: key facts and practical considerations.

- Administered orally at a dose of 50 mg twice-daily, or 50 mg daily if used in combination with a sulphonylurea.
- Reduces HbA_{1c} by approximately 0.5–0.8%.
- Generally regarded as weight neutral.
- May be used as dual therapy in combination with metformin, a sulphonylurea or a thiazolidinedione.
- A fixed-dose combination with metformin is available.
- Liver function monitoring is advised at 3-monthly intervals.
- Should not be used in people with hepatic or moderate to severe renal impairment.

Box 5. Exenatide: NICE's recommendations for use (National Collaborating Centre for Chronic Conditions, 2008).

- Consider exenatide as an option only if all the following apply:
  - A BMI >35.0 kg/m^2 in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.
  - Specific problems of a psychological, biochemical or physical nature arising from high body weight.
  - Inadequate blood glucose control (HbA_{1c} ≥7.5%) with conventional oral agents after a trial of metformin and sulphonylurea
  - Other high-cost medication, such as a thiazolidinedione or insulin injection therapy, would otherwise be started.
- Continue exenatide therapy only if a beneficial metabolic response (≥1.0% HbA_{1c} reduction in 6 months and a weight loss of ≥5% at 1 year) occurs and is maintained.

CPD module

Page points

1. The dipeptidyl peptidase-4 (DPP-4) inhibitors are generally regarded as weight neutral.
2. As with the glucagon-like peptide-1 (GLP-1) receptor agonist class of agents, a number of additional DPP-4 inhibitors are in development.
3. A short clinical guideline on the use of newer drugs for blood glucose lowering, including GLP-1 receptor agonists and DPP-4 inhibitors, is currently being prepared by NICE.

Bolli et al (2008) performed a similar 24-week trial to compare the addition of vildagliptin 50 mg twice-daily and pioglitazone 30 mg daily to metformin monotherapy. The reduction in HbA_{1c} achieved with vildagliptin was again non-inferior to that in the group receiving the TZD. Vildagliptin was not associated with a change in body weight, whereas those receiving pioglitazone gained weight.

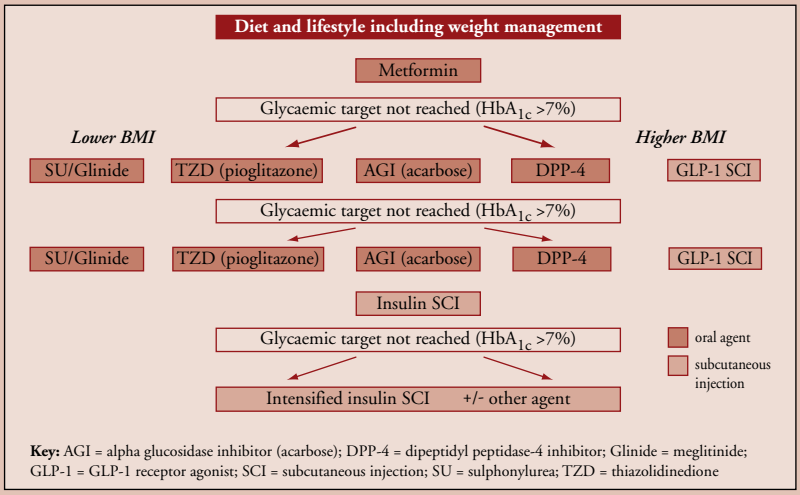
Contraindications and side-effects

The DPP-4 inhibitors are generally regarded as weight neutral (Nathan et al, 2009). Hypoglycaemia is not a significant concern, although as described above, rates of hypoglycaemia may be increased when DPP-4 inhibitors are combined with a sulphonylurea. For this reason, drivers holding Group 2 licenses who are treated with a DPP-4 inhibitor and a sulphonylurea are required to inform the DVLA (DVLA, 2008).

DPP-4 inhibitors are otherwise generally well tolerated. Reported side-effects include infections of the upper respiratory tract as well as headache. Infrequently, the class can be associated with abdominal pain, nausea and diarrhoea.

DPP-4 inhibitors: Future developments

As with the GLP-1 receptor agonist class of agents, a number of additional DPP-4 inhibitors are in development. Examples include alogliptin (DeFronzo et al, 2008), linagliptin and saxagliptin (Rosenstock et al, 2008).



Key: AGI = alpha glucosidase inhibitor (acarbose); DPP-4 = dipeptidyl peptidase-4 inhibitor; Glinide = meglitinide; GLP-1 = GLP-1 receptor agonist; SCI = subcutaneous injection; SU = sulphonylurea; TZD = thiazolidinedione

Figure 1. Algorithm for the management of hyperglycaemia in type 2 diabetes. (Feher et al, 2008; Adapted and reproduced with permission from SAGE Publications Ltd.)

Clinical use of GLP-1 receptor agonists and DPP-4 inhibitors

Current guidance from NICE regarding the use of exenatide is illustrated in *Box 5* (NCCCC, 2008). The agent is recommended as a third-line option for people meeting a range of clinical criteria. A short clinical guideline on the use of newer drugs for blood glucose lowering, including GLP-1 receptor agonists and DPP-4 inhibitors, is currently being prepared by NICE. At the time of going to press, a draft for consultation is accessible from NICE's website, with publication of the final document expected later this year (NICE, 2008). Attention is focused on the cost-effectiveness as well as therapeutic utility in these guidelines.

Other algorithms have been published that include newer agents. Emphasis is placed on the need to control weight as well as hyperglycaemia and advocates a tailored approach to therapy escalation. *Figure 1* illustrates one such example (Feher et al, 2008). Another algorithm was published in a recent supplement to this journal (Barnett et al, 2008). *Box 6* presents a case study highlighting some of the practical considerations related to the use of exenatide and the DPP-4 inhibitors.

Other agents and future developments

In addition to the incretin system-based therapies, there are a number of other blood glucose lowering agents in development that impact on varying components of glucose homeostasis. These are considered below for completeness, along with information on pramlintide, a newer agent that is commercially available in the USA.

Pramlintide

Amylin, a neuroendocrine hormone, is released from the beta-cells of the pancreas in conjunction with insulin secretion (VanDeKoppel et al, 2008). It binds to cerebral receptors and lowers glucose levels by inhibiting the secretion of glucagon. It plays an important role in the early utilisation of ingested glucose (Ludvik et al, 2003). Diminished pancreatic beta-cell function leads to decreased insulin and amylin secretion and hyperglucagonaemia. This promotes endogenous glucose production and glycogen breakdown, the net result of which is hyperglycaemia.

Pramlintide, a synthetic form of amylin, is established as a co-agent with insulin in the management of people with type 1 and type 2 diabetes (Amylin Pharmaceuticals, Inc., 2008). It has been licensed for use in the USA since 2005. Pramlintide has a favourable effect on weight loss, which is an attractive feature, but it requires administration by subcutaneous injection. In addition, it must be used in combination with insulin at mealtimes, necessitating multiple additional injections daily. The most common side-effect with pramlintide is nausea. Although pramlintide does not cause hypoglycaemia by itself, it can enhance the hypoglycaemic effect of insulin (Amylin Pharmaceuticals, Inc., 2008).

Sodium glucose co-transporter type 2 (SGLT2) inhibitors

SGLT2 inhibition has been identified as a potential mechanism for managing hyperglycaemia. Within the kidney, SGLT2 promotes the majority of glucose re-absorption (along with sodium re-absorption) from the S1 section of the proximal renal tubule. Blocking SGLT2 action leads to glycosuria and a lowering of blood glucose (Komoroski et al, 2009). SGLT2 inhibitors are currently in development for use in both type 1 and type 2 diabetes. Important side-effects of these agents include urinary tract infections, electrolyte imbalance and polyuria.

Glucokinase activators

Glucokinase activators improve glucose control through increased hepatic glucose uptake and glucose-dependent insulin secretion (Fyfe et al, 2007).

Glucagon receptor antagonists

Glucagon receptor antagonists interfere with glucagon action and promote insulin and GLP-1 production. Lowering of HbA_{1c} without hypoglycaemia and weight loss has been noted in early trials (Qureshi et al, 2004).

Selective peroxisome proliferator-activated receptor modulators (SPPARMs)

SPPARMs use adjuvant co-factors and produce fewer side-effects than TZDs, and are in a reasonably advanced stage of development (Carmona et al, 2007). It is hoped that the benefits of PPAR-gamma activation will be gained without the drawbacks of earlier agents in this class.

Box 6. Case example.

Narrative

Paul is a 55-year-old delivery driver who has had type 2 diabetes for 10 years. He is recently divorced and has two children aged 23 and 19. His father and one uncle developed type 2 diabetes in their 70s, while his sister had gestational diabetes in two of her three pregnancies. There is no family history of heart disease.

For the first 2 years after his diagnosis he managed his diabetes by diet alone. He was then put on metformin monotherapy for a further 2 years and is now taking metformin 1 g three-times daily and gliclazide 160 mg twice-daily. His other medication includes ramipril 5 mg once-daily and simvastatin 40 mg at night. He has no problem with self-monitoring of his blood glucose but has not thought seriously about injecting himself as part of his treatment. He takes little exercise and admits to eating a lot of convenience food.

His HbA_{1c} level is 8.4%. His BMI is 35 kg/m^2. His lipid profile is as follows: total cholesterol level 4.0 mmol/L; triglyceride level 1.6 mmol/L; HDL-cholesterol level 1.0 mmol/L; LDL-cholesterol level 1.8 mmol/L. His blood pressure is 138/78 mmHg. He has normal renal function. Paul's weight has increased by 6 kg since being on the highest dose of sulphonylurea, which has made him quite despondent. He feels self-conscious about his appearance, especially as he has just started a new relationship. He has no significant microvascular complications.

Discussion

Paul is typical of many people whose glycaemic control is complicated by weight gain as a result of excessive calorific intake, sedentary lifestyle and treatment with some oral blood glucose lowering agents. He is now living separately from his ex-wife and drives for a living. He has been fortunate so far not to have incurred significant macrovascular or microvascular complications.

While lifestyle changes, including appropriate dietary advice and exercise, are central to any strategy intended to help both his hyperglycaemia and weight gain other measures may be required. Insulin would help lower his HbA_{1c} closer to target but could result in weight gain or hypoglycaemia. The latter might prove very problematic in respect of his occupation. Thiazolidinediones can also effectively lower blood glucose in many people but do result in weight gain as well.

If he was reluctant to inject it might be worthwhile starting him on a dipeptidyl peptidase-4 (DPP-4) inhibitor. These oral agents can be effective glucose lowering drugs, without the disadvantage of weight gain and significant hypoglycaemia. In the future, guidelines may well advocate use of these agents immediately after metformin.

If losing weight, as well as improving glycaemic control, was his priority, and he did not mind injecting twice daily, he might well benefit from treatment with exenatide, starting at 5 µg twice-daily for 1 month and rising to 10 µg twice-daily if reasonably tolerated. A close eye would need to be kept on his blood glucose levels during the initial phase in case hypoglycaemia occurs – in which case his dose of sulphonlyurea could be halved or even stopped if necessary. (Appropriate adjustment of the regimen also applies regarding DPP-4 inhibitors.) He should be counselled about the possibility of some nausea early on in exenatide therapy. He should also be advised to stop exenatide if abdominal or back pain develops and seek expert advice directly.

CPD module

Page points

1. Account needs to be taken of many factors when deciding on optimal glucose lowering treatment for people with type 2 diabetes.
2. For those unable or unwilling to use established agents with long-term safety and efficacy data (metformin, sulphonylureas and insulin), a newer therapy may be a logical option.
3. The advent of glucagon-like peptide-1 receptor agonists presents people with an alternative injectable therapy to insulin when oral agents fail to provide adequate glycaemic control, while dipeptidyl peptidase-4 inhibitors offer an additional oral glucose lowering treatment, probably most appropriately used earlier in the disease process.

Conclusion

Account needs to be taken of many factors when deciding on optimal glucose lowering treatment for people with type 2 diabetes. These include patient preference (e.g. beliefs about insulin, injectable therapies, concerns regarding hypoglycaemia and weight management), drug tolerability and side-effects (weight and hypoglycaemic effects, as well as cardiovascular risk). For those unable or unwilling to use established agents with long-term safety and efficacy data (metformin, sulphonylureas and insulin), a newer therapy may be a logical option. The advent of GLP-1 receptor agonists presents people with an alternative injectable therapy to insulin when oral agents fail to provide adequate glycaemic control, while DPP-4 inhibitors offer an additional oral glucose lowering treatment, probably most appropriately used earlier in the disease process. ■

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Online CPD activity

Visit www.diabetesandprimarycare.co.uk/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learned in practice.

1. **When considering the incretin effect, which ONE of the following statements is true?**
   - A. An enhanced glucagon response is observed when glucose is administered orally, as compared with parenterally.
   - B. A reduced insulin response is observed when glucose is administered orally, as compared with parenterally.
   - C. A reduced insulin response is observed when glucose is administered parenterally, as compared with orally.
   - D. It is explained predominantly by glucose-dependent secretion of glucose-dependent insulinotropic polypeptide (GIP).
   - E. It is explained predominantly by glucose-independent secretion of glucagon-like peptide-1 (GLP-1).

2. **When considering the incretin system, which ONE of the following statements is true?**
   - A. GIP responsiveness is diminished in people with type 2 diabetes.
   - B. GLP-1 responsiveness is diminished in people with type 2 diabetes.
   - C. Expression of the GIP receptor may be increased in people with insulin resistance.
   - D. GLP-1 binds to the same receptors as sulphonylureas.
   - E. The insulinotropic effect of GLP-1 is independent of ambient glucose levels.

3. **GLP-1 has a number of effects in addition to stimulating insulin secretion. Which ONE of the following is not an effect of GLP-1?**
   - A. Suppression of glucagon secretion.
   - B. Induction of satiety.
   - C. Promotion of appetite.
   - D. Delayed gastric emptying.
   - E. Reduction of food intake.

4. **When using exenatide as per NICE's 2008 guidance on the management of type 2 diabetes, which ONE of the following is not a relevant condition?**
   - A. A BMI of 33 kg/m^2 in a person of European descent.
   - B. A BMI of 33 kg/m^2 in a person of south Asian origin.
   - C. Depression as a result of high body weight.
   - D. An HbA_{1c} level of 9.2%.
   - E. Pioglitazone would otherwise be initiated.

5. **When considering the advice given to a person starting exenatide therapy, which ONE of the following is incorrect?**
   - A. Injections can be given independently of mealtimes.
   - B. Gastrointestinal side-effects may occur, particularly in the early stages of treatment.
   - C. Recipients need to notify the Driver and Vehicle Licensing Agency if they are also taking a sulphonylurea.
   - D. Injections must be at least 6 hours apart.
   - E. The risk of hypoglycaemia is increased if the person is also taking a sulphonylurea.

6. **When considering sitagliptin, which ONE of the following statements is true?**
   - A. It has not been shown to improve beta-cell function.
   - B. It can be used in combination with metformin and a sulphonylurea.
   - C. It promotes the secretion of endogenous GLP-1.
   - D. It has a similar method of action to metformin.
   - E. It does not reduce fasting glucose levels compared with placebo.

7. **When considering vildagliptin, which ONE of the following statements is untrue?**
   - A. A fixed-dose combination with metformin is available.
   - B. It may be used in combination with insulin.
   - C. Liver function tests should be performed at 3-monthly intervals.
   - D. It may be used as a dual oral therapy in addition to a sulphonylurea.
   - E. It may be used as a dual oral therapy in addition to a thiazolidinedione.

8. **A 77-year-old lady who lives alone and who has a 23-year history of type 2 diabetes attends the surgery. Her current medication regimen is gliclazide 320 mg daily and extended-release metformin 500 g daily. She cannot tolerate a higher dose of metformin and has recently been treated for heart failure. She refuses to consider an injectable therapy and her last recorded HbA_{1c} is 9.1%. Which ONE of the following is the most inappropriate next management step?**
   - A. Substitution of gliclazide with repaglinide, titrating to 4 mg with main meals.
   - B. Addition of acarbose, titrating to 100 mg three-times daily.
   - C. Addition of sitagliptin 100 mg daily.
   - D. Addition of pioglitazone, titrating up to 45 mg daily.
   - E. Substitution of gliclazide with nateglinide, titrating to 120 mg three-times daily.

9. **A 67-year-old man diagnosed with type 2 diabetes 8 years ago presents to the surgery with an HbA_{1c} of 8.6% on a regimen of metformin 2 g daily and gliclazide 160 mg daily. He drives a taxi for a living and his BMI is 39 kg/m^2. He has previously had a myocardial infarction. He is prepared to accept an injectable therapy, and weight loss is his priority. Which ONE of the following is the most appropriate treatment step?**
   - A. Initiate sitagliptin.
   - B. Initiate insulin glargine.
   - C. Initiate insulin detemir.
   - D. Initiate vildagliptin.
   - E. Initiate exenatide.

10. **A 58-year-old Caucasian man with type 2 diabetes who works as a scaffolder visits your surgery. He remains active in his work and his HbA_{1c} is 8.5% on metformin 2 g daily. He has a BMI of 32 kg/m^2, and is keen to avoid further weight gain as he has recently started a new relationship. Given that hypoglycaemia poses a danger in light of his vocation, and considering NICE's 2008 recommendations on the use of exenatide, which ONE of the following options would be the most appropriate management step?**
   - A. Initiate a sulphonylurea and titrate as appropriate.
   - B. Initiate a DPP-4 inhibitor.
   - C. Initiate basal insulin and titrate as appropriate.
   - D. Initiate exenatide, titrating to 10 µg twice-daily.
   - E. Initiate a thiazolidinedione and titrate as appropriate.