

drugs very early in the disease, perhaps even in the pre-diabetic phase. This therapy would depend on favourable outcomes in long-term studies.

### Further reading

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*Professor Prins has received research funding and/or honoraria for lectures or Advisory Board membership from Merck Sharp & Dohme, NovoNordisk and Novartis.*

### Self-test questions

*The following statements are either true or false (answers on page 111)*

7. Stimulating the receptor for glucagon-like peptide causes weight gain.
8. Incretin analogues cause hypoglycaemia in patients with type 2 diabetes.



## Experimental and clinical pharmacology

### Incretin mimetics and enhancers: clinical applications

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#### Summary

**Mimicking or enhancing the actions of incretin can help to control type 2 diabetes. Exenatide and liraglutide are injectable glucagon-like peptide-1 receptor agonists, while vildagliptin and sitagliptin are oral dipeptidyl peptidase 4 inhibitors. These drugs have their main effects on postprandial glucose, but also lower fasting glucose concentrations. Glucagon-like peptide-1 agonists lower glycated haemoglobin by about 1–1.7% and induce weight loss, but frequently cause transient nausea. Dipeptidyl peptidase 4 inhibitors reduce glycated haemoglobin by 0.5–1%. They have infrequent adverse effects, but no effect on weight. Longer-term data are required to establish their full adverse event profile and their efficacy in reducing the macro- and microvascular complications of diabetes.**

Key words: dipeptidyl peptidase, glucagon-like peptide, exenatide, liraglutide, sitagliptin, vildagliptin.

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#### Introduction

The incretin effect is a normal physiological response involving gut hormones. These incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), stimulate pancreatic  $\beta$  cells to increase insulin secretion in response to oral carbohydrates. In type 2 diabetes, the secretion of GIP remains normal but the insulin response to it is impaired. GLP-1 concentrations are reduced in type 2 diabetes but the pancreatic response is relatively preserved. Using agonists to mimic the action of incretin, or inhibiting incretin metabolism to enhance the effect, are new strategies to treat type 2 diabetes.<sup>1</sup> The main effect of the drugs is to lower postprandial glucose. This is particularly attractive, as postprandial glucose concentrations are more strongly linked to cardiovascular disease than is fasting glucose.<sup>2</sup>

#### GLP-1 receptor agonists (mimetics)

GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP4), so its potential as a drug is very limited. However, drugs which are synthetic agonists at the GLP-1 receptor resist cleavage by DPP4.

#### Exenatide

Exenatide is an agonist which is administered twice daily before meals by subcutaneous injections from a pre-filled pen. The

starting dose is 5 microgram twice daily, increasing if tolerated after one month to 10 microgram twice daily. A long-acting release formulation of exenatide that is injected subcutaneously once a week has been studied.

Exenatide is cleared by glomerular filtration and while no dose adjustment is needed for mild renal impairment, exenatide probably should not be used in patients with a creatinine clearance less than 30 mL/min or on dialysis. There have been no studies in patients with liver disease and the effects on human pregnancy are unknown.

### *Efficacy of exenatide in combination with oral hypoglycaemic drugs*

Randomised placebo-controlled clinical trials have enrolled 1689 patients with suboptimally controlled type 2 diabetes despite treatment with metformin, sulfonylureas or thiazolidinediones. The metformin and/or sulfonylurea studies lasted 30 weeks and the thiazolidinedione study lasted 16 weeks. Patients were randomised to add placebo, low- (5 microgram) or high-dose (10 microgram) exenatide twice daily. The mean effects of exenatide, in comparison to placebo, were:

- a reduction in glycated haemoglobin (HbA1c) of approximately 0.6% with low dose and 1.0% with high dose (both doses resulted in significantly greater proportions of patients achieving an HbA1c of 7% or less)
- a reduction in fasting plasma glucose of approximately 1.0 mmol/L with low dose and 1.4 mmol/L with high dose
- reductions in postprandial glucose of approximately 2.0 mmol/L with low dose and 3.0 mmol/L with high dose
- progressive weight loss during the trial period, with a reduction in body weight of approximately 0.8 kg with low dose and 1.4 kg with high dose.

A total of 974 patients opted to continue exenatide in uncontrolled open-label extensions to these trials. For 283 patients follow-up lasted for two years.<sup>3</sup> During the two years the HbA1c reduction (approximately 1.0% from baseline) was sustained and weight loss continued (4.7 kg below baseline). Other statistically significant effects were increased high density lipoprotein cholesterol (0.12 mmol/L), decreased triglycerides (0.4 mmol/L) and decreased diastolic blood pressure (2.7 mmHg). The alanine transaminase concentration returned to normal in 39% of the patients who had elevated baseline concentrations.<sup>3</sup> This reduction probably reflects a decrease in liver inflammation in patients with non-alcoholic fatty liver disease.

The long-acting release formulation of exenatide has been used in a randomised placebo-controlled study of 45 patients with type 2 diabetes.<sup>4</sup> After 15 weeks of once-weekly subcutaneous injections the mean changes were:

- a reduction in HbA1c of 1.4% to 1.7% from baseline (with 0.8 mg and 2.0 mg/week respectively) compared to a rise of 0.4% with placebo

- a reduction in fasting plasma glucose of 2.4 mmol/L and 2.2 mmol/L from baseline (with 0.8 mg and 2.0 mg/week respectively) compared to a rise of 1.0 mmol/L with placebo
- weight loss of 3.8 kg in the 2.0 mg/week arm, but no change in the 0.8 mg/week or placebo arms.

### *Efficacy of adding exenatide or insulin*

In patients with suboptimally controlled diabetes despite maximal doses of metformin and a sulfonylurea, adding twice-daily exenatide was compared with adding once-daily insulin glargine.<sup>5</sup> After 26 weeks HbA1c had fallen by 1.1% in both groups. Exenatide reduced postprandial glucose more effectively and produced less nocturnal hypoglycaemia than insulin, whereas insulin reduced fasting plasma glucose more than exenatide did. Body weight decreased with exenatide (2.3 kg) but increased (1.8 kg) with insulin glargine.

Similar results were found in a 52-week open-label study comparing the addition of exenatide with the addition of twice-daily insulin aspart in patients with suboptimally controlled diabetes despite taking maximal doses of metformin and sulfonylurea.<sup>6</sup> The HbA1c reduced by approximately 1% and fasting plasma glucose by approximately 1.7 mmol/L in both groups. Exenatide produced a greater reduction in postprandial glucose and caused weight loss, whereas the patients given insulin gained weight (between-group difference 5.4 kg).

### *Safety*

GLP-1 agonists appear not to cause hypoglycaemia directly. When exenatide is added to metformin, the rates of hypoglycaemia are no different from those of adding placebo. However, when exenatide is added to a sulfonylurea, there is an increase in hypoglycaemia.

Gastric emptying is slowed by exenatide, and this may be an important part of its glucose-lowering mechanism, as it slows the absorption of carbohydrate. Gastrointestinal symptoms are common. Mild to moderate nausea is the most frequent adverse effect. The duration of nausea was not formally reported but was described as intermittent in a 16-week study. Analysis of the two-year follow-up data showed that when treatment-emergent adverse events were examined in 10-week intervals from baseline, the incidence of nausea was highest initially (39% of patients) and remained above 10% for subsequent 10-week intervals until 100 weeks had passed. However, only 3% of patients stopped exenatide because of nausea.<sup>2</sup> Weight loss was independent of the presence of nausea.

Anti-exenatide antibodies occurred in approximately 40% of patients. The antibody titre did not affect clinical efficacy, but the long-term significance of having antibodies is unknown. Injection site reactions are uncommon.

There is a possible association between exenatide use and acute pancreatitis. The incidence of acute pancreatitis with exenatide was 1.7 cases/1000 patient years in clinical development studies

and 0.2/1000 patient years during postmarketing surveillance. By comparison, the incidence was 3.0/1000 patient years with placebo and 2.0/1000 patient years with insulin.

## **Liraglutide**

Liraglutide is the second GLP-1 receptor agonist to be developed, and, like exenatide, is injectable.

### **Efficacy**

The published randomised controlled clinical trials of liraglutide monotherapy enrolled 745 patients with type 2 diabetes. These studies were phase II dose-ranging studies which lasted 5–14 weeks. Patients were randomised to use placebo, once-daily liraglutide at various doses, metformin or glimepiride. The mean effects of liraglutide, in comparison to placebo, were:

- a reduction in HbA1c at doses of at least 0.6 mg/day. This reduction was approximately 0.9% at low dose (0.6–0.75 mg/day) and 1.7% at high dose (1.9–2.0 mg/day).
- a reduction of fasting plasma glucose of approximately 2.2 mmol/L with low doses and 3.4 mmol/L with high doses
- significantly greater proportions of patients achieving postprandial glucose less than 10 mmol/L with high doses
- a weight loss from baseline of 2.5 kg with high doses.

Comparison of the effect of adding liraglutide 2.0 mg/day or adding glimepiride 4 mg to treatment with metformin showed:

- no difference in amount of HbA1c reduction
- a greater reduction in fasting serum glucose (1.2 mmol/L more than glimepiride)
- a greater reduction in postprandial glucose (1.1 mmol/L less excursion than with glimepiride)
- a reduction in body weight (1.2 kg weight loss versus 0.8 kg weight gain with glimepiride).

Unlike exenatide, there are no published studies of liraglutide combined with sulfonylureas or thiazolidinediones. No significant changes in lipids were observed with liraglutide treatment.

### **Safety**

The most frequent adverse effects of liraglutide are generally transient and include nausea, diarrhoea, vomiting and headache. With liraglutide 2.0 mg used as monotherapy or combined with metformin, the median duration of gastrointestinal events was 1–3 days, with most events reported in the first 23 days of treatment. Nausea led to withdrawal of 4% of patients from trials. The incidence of confirmed hypoglycaemia associated with liraglutide use in clinical studies was extremely low. No antibody formation has been reported so far and injection site reactions are uncommon.

## **DPP4 inhibitors (enhancers)**

The highly selective DPP4 inhibitors vildagliptin and sitagliptin prevent the normal rapid degradation of GLP-1. They are

selective because they inhibit DPP4 significantly more than the related enzymes, DPP8 and DPP9. DPP4 inhibitors have similar clinical effects to GLP-1 receptor agonists, but generally do not slow gastric emptying or lead to weight loss.

Vildagliptin and sitagliptin are administered orally once daily. Sitagliptin is 79% renally excreted, and dosage reduction is required with renal failure. Vildagliptin is mainly hydrolysed and only 22% is excreted unchanged by the kidneys, hence dose adjustments are unlikely to be needed in renal failure. No dose adjustment is required in patients with hepatic impairment.

### **Efficacy**

Published studies have examined DPP4 inhibitors as monotherapy or combined with metformin or thiazolidinediones.<sup>1</sup>

#### **Vildagliptin**

The published randomised controlled trials of vildagliptin as monotherapy or add-on therapy enrolled 5165 patients with type 2 diabetes. Most trials ran for 24 weeks (range 12–52 weeks). The mean effects of daily vildagliptin monotherapy when compared to placebo were:

- a reduction in HbA1c of 0.6% with vildagliptin 50 mg/day and 0.7% with vildagliptin 100 mg
- a reduction of fasting plasma glucose of approximately 0.9 mmol/L with vildagliptin 50 mg and 1 mmol/L with vildagliptin 100 mg. (The change from baseline fasting plasma glucose ranged from 0.4 to 0.97 mmol/L with 50 mg and from 0.8 to 1.1 mmol/L with 100 mg.)
- a placebo-adjusted reduction in 4-hour postprandial plasma glucose of 1.5 mmol/L with 50 mg and 0.9 mmol/L with 100 mg (only two studies examined this effect)
- no significant reduction in weight.

When used as add-on therapy to metformin, vildagliptin reduced HbA1c significantly when compared to placebo (by 0.7% with 50 mg and 1.1% with 100 mg). Daily doses also significantly reduced fasting plasma glucose (by 1 mmol/L with 50 mg and 1.5 mmol/L with 100 mg).

When vildagliptin was added to pioglitazone treatment, combination therapy was significantly more efficacious in improving glycaemic control than either drug alone. The combination decreased HbA1c by 0.7% (with 100 mg vildagliptin).

A single study added vildagliptin to the treatment of patients with diabetes poorly controlled by insulin. The combination only decreased HbA1c by 0.3% relative to placebo.

In active comparator studies, 100 mg vildagliptin:

- failed the statistical non-inferiority test when compared to 2 g metformin in previously untreated patients (HbA1c fell by 1.0% vs 1.4%)
- was statistically non-inferior when compared to treatment with rosiglitazone 8 mg (HbA1c fell by 1.1% vs 1.3%).

## Sitagliptin

The trials of sitagliptin included 6315 people with type 2 diabetes and mostly ran for 24 weeks (range 12–52 weeks). Doses ranged from 10 mg to 200 mg/day with 100 mg/day the most common dose. The mean effects of sitagliptin 100 mg/day monotherapy when compared to placebo were:

- a reduction in HbA1c of 0.8%
- a placebo-adjusted reduction in fasting plasma glucose of 1.1 mmol/L. (The change from baseline in fasting plasma glucose with sitagliptin was 0.8 mmol/L (range 0.7–0.94 mmol/L))
- a reduction in 2-hour postprandial plasma glucose of 3.2 mmol/L (range 2.6–4.5 mmol/L)
- no significant weight change.

When used as add-on therapy to metformin, sitagliptin 100 mg reduced HbA1c by 0.7% and fasting plasma glucose by 1.5 mmol/L, significantly more than placebo. Adding sitagliptin to metformin was not inferior to adding glipizide to metformin.

Compared to placebo, adding sitagliptin to pioglitazone treatment decreased HbA1c by 0.7% and fasting plasma glucose by 1 mmol/L. When added to glimepiride, sitagliptin 100 mg reduced HbA1c by 0.89% and by 0.6% when added to glimepiride plus metformin.

## Safety

The collective data show that vildagliptin and sitagliptin are well tolerated, with a low incidence of gastrointestinal effects or hypoglycaemia.<sup>1</sup> Adverse events reported in the clinical trials had no specific pattern and were not generally increased relative to the comparator groups. DPP4 inactivates many peptides and is identical to the T cell activation antigen CD26, so its inhibition potentially can affect many pathways. Long-term safety is unknown. Post-marketing reports of anaphylaxis, angioedema, rash, urticaria and exfoliative skin conditions such as Stevens-Johnson syndrome have occurred with sitagliptin, up to 3 months after starting treatment.

## Treatment of type 2 diabetes

Aggressive treatment of type 2 diabetes typically requires the use of multiple hypoglycaemic drugs. For type 2 diabetes that is not controlled by a sulfonylurea and metformin, or for patients unable to tolerate a sulfonylurea or metformin, the GLP-1 agonists or DPP4 inhibitors offer options for third-line therapy.

These drugs reduce postprandial and fasting glucose concentrations with sustained improvement in HbA1c, without weight gain or significant hypoglycaemia. They potentially preserve  $\beta$  cell function with chronic use and have favourable safety profiles. GLP-1 receptor agonists lead to weight loss, but frequently cause nausea, although this is often transient. Neither weight loss nor nausea occurs with DPP4 inhibitors. Until long-term data are available to confirm safety and explore

the potential for cardiovascular protection, these new drugs will inevitably be restricted to add-on therapy, with metformin remaining the first choice oral hypoglycaemic drug.

## Further research

Promising orally active GLP-1 receptor agonists include substituted quinoxalines and cyclobutanes. Long-acting GLP-1 receptor agonists, which use microspheres or albumin bioconjugates to make them suitable for once-weekly injection, are being developed.

## Conclusion

The GLP-1 receptor agonists and DPP4 inhibitors are important and promising additions to diabetes therapy which will help more patients with type 2 diabetes achieve their glycaemic targets. The results of long-term studies are required to determine adverse effects with chronic use as well as outcomes for cardiovascular events and the incidence of microvascular complications.

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## Further reading

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## Self-test questions

*The following statements are either true or false (answers on page 111)*

9. The nausea associated with exenatide can persist for more than a year.
10. The main effect of drugs acting on the incretin system is a reduction in postprandial glucose concentrations.

## New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

### Fosaprepitant dimeglumine

Emend IV (Merck Sharp & Dohme)

vials containing 115 mg as powder for reconstitution

Approved indication: chemotherapy-induced nausea and vomiting

Australian Medicines Handbook section 12.3.4

Aprepitant is an oral antiemetic which was marketed for use in chemotherapy in 2004 (see 'New drugs' 2004;27:76-9).

Fosaprepitant is an intravenous formulation of aprepitant which can be given on the first day of chemotherapy. The dose is infused over 15 minutes, 30 minutes before chemotherapy.

Fosaprepitant is a prodrug. It is rapidly converted by many tissues into aprepitant. An intravenous dose of 115 mg fosaprepitant is equivalent to an oral dose of 125 mg aprepitant.<sup>1</sup> Although the concentrations are similar after 24 hours, the maximum concentration of aprepitant is higher when fosaprepitant is used.

There appear to be few published clinical trials of fosaprepitant. Its product information only contains pivotal efficacy studies of aprepitant. The adverse effects of the two drugs are similar, but fosaprepitant has some extra warnings: the intravenous formulation is incompatible with Hartmann's or Ringer's lactate solution.

A dose of fosaprepitant does not stop vomiting, immediately after cisplatin-based chemotherapy, in as many patients

as ondansetron, but it does reduce delayed emesis.<sup>2</sup> A similar result occurred when intravenous fosaprepitant and dexamethasone, followed by oral aprepitant, were compared to ondansetron and dexamethasone, followed by placebo.<sup>3</sup>

As aprepitant is metabolised by the cytochrome P450 system, especially 3A4, fosaprepitant can interact with other drugs with similar metabolism such as cyclosporin and tacrolimus. Aprepitant can reduce concentrations of warfarin and oral contraceptives. Inhibition of P450 3A4 by ketoconazole will increase concentrations of aprepitant.

**T T** manufacturer provided additional useful information

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