Drugs for diabetes: part 6  
GLP-1 receptor agonists

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The glucagon-like peptide-1 (GLP-1) receptor agonists are a new class of injected drugs for the treatment of type 2 diabetes. They mimic the action of GLP-1 and increase the incretin effect in patients with type 2 diabetes, stimulating the release of insulin. They have additional effects in reducing glucagon, slowing gastric emptying, and inducing satiety. In clinical practice they are associated with significant reductions in glycosylated haemoglobin (HbA1c), weight loss and a low risk of hypoglycaemia. Beneficial effects have also been observed on blood pressure and lipids. The possibility of cardiovascular benefit is now being formally examined in large randomised-controlled trials with primary cardiovascular end points.

Introduction

The cardiovascular morbidity and mortality associated with diabetes are well established, so much so that type 2 diabetes has been described as a cardiovascular disease presenting as a metabolic disorder. Patients with type 2 diabetes are particularly at risk for atherosclerosis; consequently glycaemic therapies with ancillary vascular benefits are particularly useful, and the pleiotropic effects of glucose-lowering medications are of interest with regards to their effects on markers of cardiovascular health. Glucagon-like peptide-1 (GLP-1) receptors are widely expressed in a number of tissues including the myocardium and cardiovasculature, and GLP-1 appears to have a range of neurotrophic, neuroprotective and cardioprotective effects. As a consequence there may be potential therapeutic benefit from these drugs.

Pharmacology

The incretin effect was described in the previous review of dipeptidyl peptidase-4 (DPP-4) inhibitors.¹ The incretin effect is reduced in patients with diabetes. DPP-4 inhibitors inhibit the breakdown of native GLP-1, increasing its concentration and, thereby, increasing the physiological effect of GLP-1 on glucose-stimulated insulin release. GLP-1 receptor agonists are an alternative treatment to pharmacologically enhance the release of insulin, with additional effects on reducing glucagon release, increasing satiety, and increasing gastric emptying (figure 1).

GLP-1 analogues mimic endogenous GLP-1 activity but are resistant to DPP-4 deactivation, resulting in prolonged activity. They cannot be administered orally, the current preparations being subcutaneous injections. Two GLP-1 agonists are currently available: exenatide, which has a half-life of four hours and requires twice-daily injection,² and liraglutide, which has a half-life of 11–13 hours and requires once-daily injections.³ A long-acting, once-weekly formulation of exenatide has recently been granted marketing authorisation by the licensing authority in Europe.

Mild-to-moderate nausea is the most common side effect associated with the use of these drugs. This was reported by about 50% of subjects in studies but declined after the first eight weeks of treatment. Only 4% of patients withdrew from trials as a result of more severe gastrointestinal side effects, including vomiting. In routine clinical practice, around one in 10 patients cannot continue with treatment because of gastrointestinal side effects. Severe hypoglycaemia is rare, and has only occurred when prescribed in combination with a sulphonylurea.

Guidelines from both the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) have...
Trials of safety and efficacy
Evidence for improved glycaemic control
In placebo-controlled, randomised trials, both exenatide and liraglutide reduce glycosylated haemoglobin (HbA1c) by about 1% when used in combination with metformin and/or sulphonylureas (and in combination with metformin and a thiazolidinedione for liraglutide). In a head-to-head study, liraglutide was more effective than exenatide twice daily in reducing HbA1c. After 26 weeks, once-daily liraglutide reduced HbA1c from 8.2% to 7.1%, with twice-daily exenatide reducing HbA1c from 8.2% to 7.4%. Weight reduction was similar with the two treatments at around 3 kg, but there was less persisting nausea with liraglutide. In a recent study, liraglutide once daily was also more effective than the twice-daily regimen. In a recent study, liraglutide was similar with the two treatments at around 3 kg, but there was less persisting nausea with liraglutide.

Evidence for cardiovascular effects
Initial animal studies of GLP-1 agonist therapy suggested varying effects on blood pressure. In humans, GLP-1 and GLP-1 agonists tend to cause a small reduction in blood pressure, although it remains to be seen whether this will be of clinical significance. The Liraglutide Effect and Action in Diabetes (LEAD) trial reported reductions of 3.6 mmHg to 6.7 mmHg in systolic blood pressure in the liraglutide-treated group compared with those treated with other agents or placebo. Interestingly, these blood pressure reductions were observed prior to weight loss, suggesting that the effects on blood pressure are independent of weight reduction. Exenatide treatment has also been shown to be associated with beneficial effects on systolic blood pressure. The mechanisms by which GLP-1 agonist therapy may reduce blood pressure remain unclear. Postulated theories include improvements in endothelial function leading to improved vasodilatory capacity and enhanced urinary sodium excretion.

GLP-1 receptor agonists have been shown to modify some inflammatory mediators and markers of vascular risk, although larger trials of longer duration will be required to confirm these preliminary findings. Significant reductions in high-sensitivity C-reactive protein (hsCRP) and improved insulin sensitivity have been reported in human subjects with type 2 diabetes treated with exenatide compared with treatment with glibenclamide, despite similar effects on HbA1c.

In addition, a meta-analysis of six phase III trials of liraglutide reported a significant 23.1% reduction in hsCRP following treatment. Other small studies have observed beneficial effects of GLP-1 infusions on other markers such as tumour necrosis factor alpha (TNFα) and venous occlusion plethysmography.

Both liraglutide and exenatide have been shown to have a beneficial effect on both fasting and post-prandial lipid profiles in type 2 diabetes. One of the largest recent studies randomised 533 subjects to liraglutide or placebo (in combination with metformin and rosiglitazone), and demonstrated significant reductions in serum low-density lipoprotein (LDL)-cholesterol, free fatty acids and triglycerides in the treatment group when compared with placebo. These findings have been replicated in other smaller studies. Infusions of GLP-1 have also been shown to improve post-prandial lipaemic excursions, an independent risk factor in the development of atherosclerotic cardiovascular disease.

GLP-1 receptors are expressed on cardiac tissue, therefore, it is possible that the hormone, or its synthetic analogues, may directly mediate a range of cardiac functions. Current areas of research include the investigation of GLP-1 involvement in myocardial metabolism, coronary blood flow, pre-/post-ischaemic conditioning, left ventricular (LV) remodelling and LV performance. Both animal and human studies have suggested that GLP-1 agonists may have effects on myocardial metabolism, and this may be translated into possible therapeutic benefit on cardiac function. Animal studies have demonstrated improved glucose utilisation and reduced accumulation of lactate in the myocardium following infusions of GLP-1 agonist. Improvements in LV function have been demonstrated in animal studies, but results from a few small studies in humans have shown conflicting results.

In addition, an animal study suggested that GLP-1 may have effects on coronary blood flow and protect against ischaemia and reperfusion injury. These findings in rodents require further work before conclusions can be drawn.

Discussion
If an individual with type 2 diabetes is able to tolerate GLP-1 receptor agonist therapy then the early clinical beneficial effects on HbA1c, weight and blood pressure may be substantial. The possible direct benefits on the heart and vascular system in animals and humans require further study and
addition, the Food and Drug Administration (FDA) has requested extra safety data for once-weekly exenatide to ensure that possible accumulation of the drug in patients with renal impairment does not affect the QT interval.

Taspoglutide was a weekly GLP-1 receptor agonist at a late stage of development. A dedicated cardiovascular safety study (T-emerge B) was underway when the whole drug development programme was halted because of allergic reactions at injection sites. Several other daily and weekly GLP-1 receptor agonists are in development and will also be required to demonstrate proof of cardiovascular safety, either in a dedicated cardiovascular safety trial or by enrolling patients at high cardiovascular risk in the phase III development programme.

**Conflict of interest**

GMcK has served on advisory boards for Eli Lilly. MF has served on advisory boards for Eli Lilly, GlaxoSmithKline, Novo Nordisk, Roche and Sanofi Aventis. CH: none declared.

**Key messages**

- Glucagon-like peptide-1 (GLP-1) receptor agonists are a new class of injected drugs for type 2 diabetes that mimic GLP-1 and increase the release of insulin in response to a meal.
- In clinical practice they cause weight loss, with a very low incidence of hypoglycaemia as a side effect.
- Short-term clinical trials have demonstrated additional beneficial effects of GLP-1 receptor agonists on blood pressure and lipids.
- The results of long-term safety studies and cardiovascular end point studies will determine the future role of these drugs.

**References**