New drugs for the treatment of type 2 diabetes

Insights into the pathogenesis of type 2 diabetes has led to increasing therapeutic targets for intervention, and improvements in peptide delivery technology have lead to non-injection methods of insulin delivery. This article reviews new drugs which are likely to become available for use by people with diabetes over the coming year.

Type 2 diabetes is one of the most pressing public health issues worldwide. The condition is responsible for significant morbidity and premature mortality, and it is now widely recognized that cardiovascular risk modification is the cornerstone of diabetes treatment.

Achieving tight glycaemic control remains a major goal of therapy to reduce the onset of microvascular disease (United Kingdom Prospective Diabetes Study (UKPDS) Study Group, 1998). Treatment for glycaemic control has relied upon a number of standard therapies (insulin, sulphonylureas and biguanides) for many years, although prandial glucose stimulators (repaglinide, nateglinide), alpha-glucosidase inhibitors (acarbose) and, more recently, thiazolidinediones (rosiglitazone and pioglitazone) have become further therapeutic options, with the latter in particular having established an important role in the management of type 2 diabetes.

The condition is inexorably progressive, with most patients ultimately requiring insulin therapy (Wright et al, 2002). Advances in knowledge of the pathogenesis of the condition has enabled a number of new classes of agent to be developed, which may enable improvement in glycaemic control, and perhaps attenuate progression of the condition.

This article will review some of the new therapies that are, or shortly will be, available for use in patients with type 2 diabetes, outlining their mechanism of action, efficacy, adverse effects and place in the treatment of patients with type 2 diabetes (*Table 1*).

Table 1. New drugs for diabetes

Name of drug	Class/mode of action	Place in therapy
Exubera	Inhaled insulin	Needle phobia or injection site problem
Rimonabant	Endocannabinoid-1 receptor antagonist	Diabetes and obesity. Adjunct to metformin
Exenatide	Glucagon-like peptide-1 agonist	Diabetes and obesity. ? In place of insulin in obese diabetic subjects
Sitagliptin Vildagliptin Saxagliptin	Dipeptidylpeptidase-IV antagonists	Diabetes and obesity. Adjunct to metformin
Pramlintide	Amylin analogue	Post prandial hyperglycaemia in insulin-treated patients
Ruboxistaurin	Protein kinase C-β inhibitor	Microvascular complications – retinopathy/ nephropathy in addition to improved glycaemic control

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Inhaled insulin

Drug name: Exubera (Pfizer, Surrey, UK)

Mode of action

The potential for inhaling insulin was first suggested in the 1920s, when it was recognized that the large surface area, rich blood supply and thin alveolo-capillary membrane of the lungs would make them an excellent site for drug delivery. Improvements in inhaler and aerosol technology have recently enabled this method of delivery to become a reality. One of the major barriers, consistency of particle size between 1 and 5 μm, has reliably been achieved; smaller size leads to exhalation of the drug, and larger leads to failure to reach the alveolus.

Two main formulations have been developed; dry powder and liquid aerosol, of which Exubera, a dry powder preparation, was the first to launch. The pharmacokinetic profile of inhaled insulin is interesting: onset of action appears to be similar to analogue insulins (lispro or aspart), but offset is comparable to that of standard human insulin. Dosing of inhaled insulin differs from that of subcutaneous insulin, as the bioavailability of inhaled insulin is only around 10% of the subcutaneous dose. Dosing is in 1 mg or 3 mg doses (1 mg = three units and 3 mg = eight units of subcutaneous insulin). Interestingly, three consecutive inhalations of 1 mg blisters results in a higher insulin level than the inhalation of a single 3 mg blister, as there is a 40% higher bioavailability of the 1 mg dose.

Efficacy

Inhaled insulin is as efficacious as subcutaneous insulin in randomized controlled trials in patients with type 1 and type 2 diabetes. In type 1 diabetes, two studies of over 300 patients have shown similar reductions in gly-

cated haemoglobin (HbA_{1c}) to subcutaneous insulin, with some improvement in fasting and post-prandial hyperglycaemia compared to standard subcutaneous insulin (Skyler et al, 2005). In type 2 diabetes, comparison with twice daily mixed insulin has shown similar reductions in HbA_{1c}, with fewer hypoglycaemic events in the inhaled group (Hollander et al, 2004). When added to dual therapy with oral agents (sulphonylurea or prandial glucose regulator, plus metformin or thiazolidinedione), a 1.9% reduction in HbA_{1c} was seen compared with oral agents alone (Rosenstock et al, 2005). Unsurprisingly, patient satisfaction with inhaled insulin was higher, as was willingness to start insulin.

Adverse effects

As with subcutaneous insulin, hypoglycaemia and weight gain are common, and similar in degree to subcutaneous insulin. More concerning are the effects on lung function.

Cough is common, occurring in around 25% of patients, usually within seconds or minutes of inhalation, although discontinuation because of this symptom was uncommon (<1%). Nevertheless, patients need counselling that this is likely to occur. Changes in pulmonary function are potentially the most important adverse effect. A small, early decline in lung function (85 ml *vs* 36 ml for Exubera *vs* subcutaneous insulin at 2 weeks) is seen, and the differences remain throughout period of administration, but reverse when inhaled insulin is discontinued. Few long-term exposure data are available, but the decline does not appear to increase beyond 3–6 months, and there is no evidence of airways sensitization. There are currently no data on potential long-term sequelae of inhaled insulin on the lung, and this will need careful post-market surveillance. Nevertheless, careful monitoring of lung function is mandatory, and stipulated in the product license, with FEV_1 (forced expiratory volume in 1 second) monitoring before, and periodically after commencing Exubera treatment.

The development of insulin antibodies has been reported with inhaled insulin, which thus far do not appear to be clinically significant. Levels decline after discontinuation of Exubera, and there appears to be no correlation between insulin antibody levels and diabetes control or insulin dose.

Cost

Approximately £1100 per annum (pa) including costs of monitoring, which is almost twice that of subcutaneous insulins widely used in UK (insulin glargine 60u daily via pen = £561.60 pa, Novomix 30 flexpen 60u daily = £460.80 pa).

Place in therapy

Exubera is licensed for the treatment of adult patients with type 2 diabetes inadequately controlled with oral antidiabetic agents and requiring insulin therapy, and for patients with type 1 diabetes mellitus to use in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns. Absolute contraindications include active smokers (more rapid absorption – must have given up at least 6 months before starting), and the presence of moderate to severe underlying lung disease.

The National Institute for Health and Clinical Excellence (NICE) is currently assessing the cost benefit of inhaled insulin. Figures on cost benefit of inhaled insulin provided by the company (quality-adjusted life years) have been disputed by NICE, and subject to re-analysis. As a result current recommendations are that inhaled insulin is a treatment option in patients with type 1 or type 2 diabetes and poor glycaemic control (HbA_{1c} >9%), who are unable to start or intensify insulin therapy because of either proven injection phobia diagnosed by a psychiatrist, psychologist or a consultant diabetologist, or severe lipohypertrophy. Treatment may only be continued longer than 6 months if a >1% reduction in HbA_{1c} is achieved. Initiation of inhaled insulin treatment and monitoring of response should be carried out only by a specialist centre, and data on outcomes should be collected as part of a prospective observational study.

In the long term, the place of inhaled insulin is far from clear. In clinical practice, genuine needle phobia is rare, although delay in commencement of insulin because of insulin reluctance is not uncommonly encountered. The significant extra cost is likely to diminish as more devices and formulations come on to the market, and it is likely that inhaled insulin will be a more available treatment option for early use of insulin in the future.

Endocannabinoid-1 receptor antagonists

Drug name: Rimonabant (Acomplia, Sanofi-Aventis, Surrey, UK)

Mode of action

Overactivation of the endocannabinoid system has been implicated in the pathogenesis of obesity (Cota et al, 2003a). Cannabinoid (CB1) receptors are G-protein coupled, and expressed in various organs, including the autonomic nervous system, liver, muscle, gastrointestinal tract and adipose tissue. Administration of cannabinoids increases food intake in satiated rodents, and CB1 knockout mice have leaner body composition (Cota et al, 2003b). Stimulation of peripheral CB1 receptors in adipocytes promotes lipogenesis and inhibits adiponectin production, leading to increase insulin resistance, while central CB1 receptor stimulation increases feeding.

Rimonabant is the first selective CB1 receptor blocker, reducing over-activation of central and peripheral CB1 receptors. Animal studies show reduced food intake and weight loss with this drug.

Efficacy

In 1045 patients with type 2 diabetes, in conjunction with a 600 kcal hypocaloric diet, 5.3 kg mean weight loss was achieved with 20 mg rimonabant, compared to 1.45 kg with placebo, along with a 5.2 cm reduction in waist circumference compared to 1.9 cm on placebo (Scheen et al, 2006) over 1 year. HbA_{1c} fell by 0.6% (baseline 7.3%), compared with a 0.1% increase on placebo. Of patients on rimonabant 43% achieved an HbA_{1c} level below 6.5% compared to 21% on placebo ($P<0.05$).

Adverse effects

Similar to many obesity studies, the drop-out rate from the Rimonabant in Obesity studies was high at 1 year (around 15%) (Scheen et al, 2006), although all results are reported as intention to treat. The most frequent adverse events were depression (2.9%), anxiety (1.7%), and nausea and dizziness (1.2%). The concerns about depression and anxiety have increased (Anonymous, 2006). Withdrawal of antiobesity agents may lead to rebound weight gain in some subjects.

Cost

The annual cost is £662.40 (compared to an annual cost of orlistat £474.12, and of sibutramine £595.80).

Place in therapy

Treatment of obese patients with type 2 diabetes is a therapeutic challenge, and many therapies which improve glycaemic control can lead to weight gain. Rimonabant adds an important therapeutic option in the treatment of obesity, and in the treatment of obese patients with type 2 diabetes. Its licence reflects this, as it can be used in patients with type 2 diabetes, and body mass index >27 kg/m^2. Its significant cost makes its widespread use difficult. It may be preferable to use rimonabant in place of sibutramine in obese patients, particularly as hypertension can be problematic with the latter. It is clear, however, that treatment with rimonabant must be accompanied by careful dietary counselling as it only works well with good dietary compliance. NICE are likely to review rimonabant in the near future.

Glucagon-like peptide-1 agonists

Drug name: Exenatide (Byetta; Lilly, Basingstoke, UK), Liraglutide (Novo Nordisk, Crawley, UK)

Mode of action

The incretin effect describes the observation that insulin response to oral glucose is greater than that of an equivalent intravenous dose (Perley and Kipnis, 1967). This is attributed to the insulinotropic effects of gut-derived peptides, in particular glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), released by endocrine cells in the gut in response to food intake (Creutzfeld, 1979). People with type 2 diabetes have significant reductions in the levels of meal-stimulated GLP-1, and administration of GLP-1 leads to increased insulin release and glucose reduction after food (Zander et al, 2002). GLP-1 appears to exert its glucose-lowering effects by enhancing glucose-dependent insulin release (particularly first phase insulin release by a direct effect on pancreatic beta cells), suppressing inappropriate glucagon release, inhibiting appetite and reducing gastric emptying. GLP-1 has an extremely short circulating half life as a result of its rapid breakdown by the enzyme dipeptidylpeptidase-IV (DPP-IV).

Exendin-4, isolated from the salivary glands of the Gila monster (*Heloderma suspectum*), is a GLP-1 analogue, exhibiting similar insulinotropic effects to GLP-1 (Eng et al, 1992). Exendin-4 has 50% homology with GLP-1, but is resistant to DPP-IV breakdown, and hence has a prolonged action of at least 6 hours post administration.

Efficacy

The commercial preparation of exendin-4, exenatide, is administered by subcutaneous injection twice daily before breakfast and the evening meal. It is supplied in a reusable pre-filled pen device, at a fixed dose of 5 or 10 µg. Treatment of patients with inadequate glycaemic control on metformin monotherapy, sulphonylurea monotherapy or combination of the two, has shown reductions in HbA_{1c} of approaching 1%, and a 2–3 kg weight loss (Buse et al, 2004; DeFronzo et al, 2005; Kendall et al, 2005). Comparison of the addition of exenatide or insulin glargine to patients inadequately controlled on metformin and/or sulphonylurea showed similar reductions in HbA_{1c} (~1%), but insulin glargine-treated patients gained a mean of 1.8 kg, while exenatide-treated patients lost a mean of 2.3 kg (Heine et al, 2005).

Of the 1125 patients who completed the 30-week studies, 87% elected to participate in open-label extension studies, which showed a sustained reduction in HbA_{1c} of 1.1%, and a continued reduction in body weight to a mean loss of 4.5 kg (Blonde et al, 2005).

Liraglutide is a GLP-1 receptor agonist, administered by once-daily injection. The drug is entering phase III studies, although small phase II studies suggest a reduction in HbA_{1c} of 0.75%, with 0.39 kg weight reduction over 12 weeks (Madsbad, 2004).

Adverse effects

Nausea is widely reported with exenatide, with around 40% of people experiencing this at initiation. The side effect tends to reduce with continued use, and can be minimized by slow dose titration. Hypoglycaemia is rare in combination with metformin, but widely reported in combination with sulphonylurea, and may necessitate a reduction in dose of the sulphonylurea.

Cost
As yet unknown.

Place of therapy
GLP-1 analogues show promising results in improving glycaemic control and reducing weight in patients with poorly controlled type 2 diabetes. As stated before, most treatments to improve glycaemic control have the disadvantage of weight gain, while these drugs appear to enable improvement in glycaemic control coupled with weight loss. In addition, the lack of dose titration makes the drug easier to teach, and less follow up nurse time will be required. The disadvantage of twice-daily injections may be obviated by the development long-acting injection (exenatide LAR) which appears to be on the horizon.

Dipeptidylpeptidase-IV antagonists

Drug name: Sitagliptin (Januvia; Merck, West Drayton, UK), Vildagliptin (Galvus; Novartis, Camberley, UK), Saxagliptin (Bristol Myers Squibb, Uxbridge, UK)

Mode of action
DPP-IV is the main proteolytic enzyme which inactivates endogenous GLP-1. Inhibitors of this enzyme have been developed which can be administered orally. In animal models, this leads to increased levels of endogenous GLP-1, and some improvement in prandial insulin release, glucose control, HbA_{1c} and improves islet survival and beta cell mass (Pospisilik et al, 2003). DPP-IV inhibitors or 'gliptins' are a new class of oral hypoglycaemics now available for type 2 diabetes.

Efficacy
In two short-term double-blind studies around 750 patients with mild to moderate glycaemic control (HbA_{1c} mean 8.0%), sitagliptin 100 mg daily showed a mean of around 0.8% HbA_{1c} reduction *vs* placebo (Aschner et al, 2006). Added to patients inadequately treated with metformin or pioglitazone alone, sitagliptin led to a 0.7% HbA_{1c} reduction (Charbonnel et al, 2006).

Twelve-week administration of vildagliptin to patients with type 2 diabetes appears to result in a 0.7% reduction in HbA_{1c}, and no weight change, and an improvement in beta cell function (Ahren et al, 2004).

Adverse effects
Nausea is common, although this is mild, and rarely leads to discontinuation. Despite the ubiquitous nature of this enzyme, there appear to be few safety concerns in trials so far.

Cost
As yet unknown, although sitagliptin has been launched in the USA at $4.86 per 100 mg tablet, equating to a yearly cost of around £900.00. Older oral therapies are relatively inexpensive (metformin 100 mg twice daily = £38.60 pa, gliclazide 160 mg twice daily = £44.80 pa, pioglitazone 45 mg = £482 pa).

Place of therapy
Sitagliptin has recently been approved for use in the USA, and is likely to be launched in Europe shortly. The development of an additional class of oral hypoglycaemic agent with few side effects and no weight gain is a welcome addition to the therapeutic armamentarium. Larger scale outcome trials will, however, be required in order for these drugs to be widely used. They may be used second or third line to metformin or glitazones.

Amylin analogues

Drug name: Pramlintide (Symlin – Amylin Pharmaceuticals, San Diego, USA)

Mode of action
Islet amyloid polypeptide, or amylin, is co-secreted with insulin from islet beta cells, in response to glucose. Amylin secretion is also stimulated by glucagon, GLP-1, and inhibited by insulin. Amylin has a glucoregulatory role, by inhibiting gastric emptying, reducing glucagon release and inhibiting food intake.

Efficacy
The amylin analogue, pramlintide, is approved for treatment of type 1 and insulin requiring type 2 diabetes in the USA. Effects on glycaemic control are modest – in type 1 diabetes, HbA_{1c} reductions of 0.3% are achieved, with around 1.5 kg weight loss (Whitehouse et al, 2002). In type 2 diabetes, 0.4% HbA_{1c} reduction is achieved, with around 2.5 kg weight loss (Hollander et al, 2003). In particular, postprandial hyperglycaemia appears to be improved by pramlintide.

Adverse effects
Nausea is a common side effect, which can be reduced with gradual dose titration. Post-prandial hypoglycaemia can be problematic if the dose of insulin is not adjusted.

Cost
As yet unknown.

Place of therapy
Pramlintide appears to have found a niche in the US in type 1 patients with problematic post prandial hyperglycaemia. Co-administration with prandial insulin can improve post-prandial excursions considerably. Despite having been available for some time, the drug is not widely used as yet, because of its modest effects.

Protein kinase C inhibitors

Drug name: Ruboxistaurin (Arxxant; Lilly, Basingstoke, UK)

Mode of action
Despite diabetic retinopathy being the commonest cause of blindness in people of working age in the UK, and

nephropathy being the commonest cause of renal failure, the mechanisms by which hyperglycaemia leads to microvascular complications are poorly understood. There is some evidence for a role of hyperglycaemia-induced diacylglycerol synthesis leading to activation of protein kinase C-β (PKC-β) (Scheetz and King, 2002). PKC-β increases retinal vascular permeability and neovascularization in when injected into the retina of diabetic rats. PKC activation is a key step in intracellular signalling of vascular endothelial growth factor (VEGF), which is thought to be a mediator of retinal permeability and neovascularization (Xu et al, 2004).

Ruboxistaurin is a PKC-β inhibitor, which has been shown to ameliorate diabetic microvascular complications in animal models, including retinopathy, neuropathy and nephropathy.

Efficacy

In a multicentre randomized placebo controlled study, 252 patients with moderate to severe diabetic retinopathy were randomized to placebo, or three doses of ruboxistaurin (8, 16 or 32 mg) for a mean of 40 months (PKC-DRS Study Group, 2005). Ruboxistaurin did not reduce progression of diabetic retinopathy, but did reduce the risk of visual loss (10% in ruboxistaurin treated *vs* 25% in placebo – 35% risk reduction). Small clinical studies of nephropathy have shown a favourable effect on estimated glomerular filtration rate and albumin creatinine ratio, although larger phase III studies are awaited.

Adverse effects

Ruboxistaurin appears well tolerated, with few side effects.

Cost

As yet unknown.

KEY POINTS

- Type 2 diabetes is a major cause of mortality and morbidity particularly from vascular disease.
- Inhaled insulin is available, but in the UK is restricted to patients with needle phobia and injection site problems. Careful monitoring of FEV_1 (forced expiratory volume in 1 second) is required.
- Rimonabant is effective at reducing weight in obese patients with diabetes, but anxiety and depression may be an important adverse effect.
- Incretin mimetics (glucagon-like peptide-1 analogues) and incretin enhancers (gliptins) are major advance in treatment, coupling improved glycaemic control with evidence of weight loss.
- Protein kinase C-β inhibitors are the first of a new group of drugs specifically targeting microvascular complications.

Place of therapy

The greatest effect of ruboxistaurin in retinopathy was seen in patients who improved glycaemic control, suggesting that stabilization of retinopathy may be achieved by a combination of medical therapy and improving glycaemic control. While early studies are encouraging, further large scale studies will be needed to determine the place of this therapy in patients with microvascular disease.

Conclusions and the future

The large numbers of people developing type 2 diabetes will lead to huge pressure on health-care systems, dealing with the high rate of attrition seen with this condition. With significant improvements in understanding of the pathogenesis of diabetes, coupled with rapid improvements in drug development and delivery technology, newer therapeutic options have become a reality. Therapies targeting the incretin hormone axis hold great promise, as do drugs acting on novel receptor systems such as the endocannabinoid system. A whole new therapeutic area – drugs to treat microvascular complications – is heralded by the development of PKC-β antagonists.

While these and many other new therapies are in development, the outlook for the treatment of this important condition appears to be improving. **BJHM**

Conflict of interest: Dr Chowdhury has been involved in clinical trials of inhaled insulin, CB1 antagonists and DPP-IV inhibitors. Dr Hossain has no competing interests.

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