Treatments and devices for future diabetes management

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This last article in this three-part series discusses the evolution of diabetes therapy and examines new treatments and delivery devices that are under development to help meet treatment and management targets.

This is the last part of a three-part series on diabetes. The first discussed how to diagnose diabetes and the second discussed the management of diabetes in advanced terminal illness.

The incidence of diabetes, particularly type 2 diabetes, is growing rapidly in the UK. This means that the effective management of diabetes and its associated complications is now a key priority.

**Management goals**

Two landmark studies, the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes (Diabetes Control and Complications Trial Research Group, 1993) and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes (UKPDS, 1998) demonstrated conclusively that achieving tight glycaemic control is an important factor for reducing the risk of long-term vascular complications and improving patient outcomes.

This therapeutic goal, together with the importance of providing optimal complete diabetes care and patient education, is reflected in documents such as the National Service Framework for Diabetes: Standards (Department of Health, 2001), National Institute for Clinical Excellence guidelines (NICE, 2002) and the new general medical services contract (British Medical Association, 2003). The past 10 years have seen an explosion in the number of new treatments available for diabetes and there are a number of exciting new drugs in development to achieve these goals.

**Evolution of treatments**

**Oral hypoglycaemic agents**

Second-generation sulphonylureas, including glipizide, glimepiride and gliclazide, became widely available in the early 1990s. These are as effective at lowering glucose levels, but are designed to have a shorter duration of action and so are associated with a reduced risk of hypoglycaemia (Lebovitz, 1999). New formulations of the second-generation sulphonylureas are also in preparation. For example, extended release glipizide allows effective once-daily rather than twice-daily dosing (Simonson et al, 1997).

A new class of oral hypoglycaemic agents (OHAs), the meglitinides or prandial glucose regulators, became available in the UK in 1998. The two approved for use in the UK are repaglinide, which is indicated for use as monotherapy, and nateglinide, which is indicated for use in oral combination regimens. As with sulphonylureas, meglitinides improve insulin secretion by β-cells. Meglitinides specifically improve early-phase insulin secretion and have a quicker onset and shorter duration of action than sulphonylureas, and so may reduce the risk of hypoglycaemia (Tankova et al, 2003).

The glitazones (thiazolidinediones) are a recent addition to oral diabetes therapy. The two glitazones available in the UK are rosiglitazone and pioglitazone. They work by improving insulin sensitivity at target tissues and are effective at lowering glucose concentrations. Their properties as insulin sensitisers mean that in addition to treating hyperglycaemia, they may also be effective at treating the characteristics of the ‘metabolic syndrome’, such as raised blood pressure and dyslipidaemia (Gale, 2001).

It is important to note that, currently, NICE recommends the use of glitazones only in patients who are contraindicated or have tolerability issues with ‘first-line’ therapies such as metformin and sulphonylureas. They are also contraindicated for use with insulin therapy in the UK. Glitazones also commonly need to be taken for at least six weeks before any clinical benefits are observed.

The most recent class of OHA is alpha-glucosidase inhibitors. Currently, only acarbose is licensed in the UK – used either alone, as an adjunct to diet and lifestyle advice or in combination with other OHAs. They work by reducing post-meal hyperglycaemia by blocking the enzymes responsible for polysaccharide digestion. They are less effective at reducing glucose concentrations but have a lower risk of hypoglycaemia compared with other OHAs. The main side-effects are gastrointestinal intolerance, such as flatulence, abdominal pain and diarrhoea (Santeusanio and Compagnucci, 1994).

This is the third in a three-part series examining issues in the care of patients with diabetes.

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**REFERENCES**


Advances in insulin therapy

In the 1990s, the rapid-acting insulin analogues insulin lispro and insulin aspart became available in the UK (Lindholm and Jacobsen, 2001). A third, insulin glulisine, developed by Sanofi-Aventis, has recently received its marketing authorisation from the European Medicines Evaluation Agency (EMEA) and is expected to become available in the UK. The rapid-acting analogues have been designed to be shorter-acting than RHI and match more closely the endogenous secretion of insulin in healthy people during mealtimes.

Their improved pharmacokinetic profile means that they can be given immediately before or after a meal. Consequently, they are more convenient for the patient compared with RHI, which should be given about 15-30 minutes before eating.

Clinical studies have also shown that rapid-acting analogues are associated with lower post-meal hyperglycaemia and a reduced risk of hypoglycaemia (Lindholm and Jacobsen, 2001).

Using similar DNA recombinant technology, the long-acting basal insulin analogues insulin glargine and insulin detemir have recently been produced and are available in the UK. These long-acting insulin analogues have been developed to match more closely the physiological profile of background insulin secretion compared with older basal insulins such as NPH.

NPH is effective at lowering HbA1c levels and, as it has been available for over 50 years, health care professionals are confident in adjusting dosages to meet individual requirements. However, the absorption profile of NPH does not match accurately that of endogenous basal insulin secretion.

After administration, plasma concentrations of NPH reach peak levels within 4-6 hours before falling below physiologically effective concentrations after 12-14 hours (Lepore et al, 2000). Consequently, patients are at risk of experiencing nocturnal hypoglycaemia but hyperglycaemia at breakfast time. Excessive weight gain is also a problem in some patients.

**BOX 1. MANAGEMENT GOALS**

- The National Service Framework for Diabetes defines poor glycaemic control as glycated haemoglobin (HbA1c) levels above 7.5% and states that these patients be treated as priority cases.
- NICE guidelines recommend a target HbA1c of 6.5-7.5% for all patients with diabetes.
- GMS contract awards 16 points to practices achieving HbA1c levels below 7.5% in 50% of patients.

Compared with NPH, insulin glargine has a more predictable and consistent rate of absorption, with a ‘peakless’ activity profile over 24 hours that allows once-daily dosing (Lepore et al, 2000). This improved pharmacokinetic profile has been shown to translate into clinical benefits compared with non-analogue basal insulins. Trials in patients with type 1 diabetes show insulin glargine results in significantly lower fasting blood glucose (FBG) concentrations compared with NPH, with significantly less weight gain and a significantly reduced risk of hypoglycaemia (Ratner et al, 2000; Rosenstock et al, 2000). A recent trial comparing a full analogue basal-bolus regimen of insulin glargine and insulin lispro with a basal-bolus regimen of NPH and RHI found patients receiving the analogue regimen had significantly lower HbA1c levels (Ashwell et al, 2003). Similarly, trials involving patients with type 2 diabetes show insulin glargine has a similar safety profile to NPH and is at least as effective at lowering HbA1c, but that patients experience significantly less hypoglycaemia and weight gain (Rosenstock et al, 2001).

Insulin detemir has also been designed to have a more consistent rate of absorption and match endogenous basal insulin secretion more closely than older basal insulins. Insulin detemir is currently only licensed for use in a basal-bolus insulin regimen and not in combination with OHAs. At present it will be used mainly in type 1 diabetes. Clinical trials in type 1 diabetes show insulin detemir, usually given twice-daily, is as effective as NPH in achieving glycaemic control but is associated with a decreased risk of hypoglycaemia and weight gain (Vague et al, 2003; Hermansen et al, 2001).

**Future treatments for diabetes**

**Combination oral tablets**

Oral medications are now available that combine two OHAs into one pill. Such formulations are more convenient as they reduce the ‘pill burden’. The first combination pill, launched in the UK in November 2003, combined a glitazone (rosiglitazone) with metformin. Two combination pills that combine a sulphonylurea (either glyburide or glipizide) with metformin have also recently been made available in the UK.

**Glucagon-like peptide-1**

The naturally occurring hormone, glucagon-like peptide-1 (GLP-1), stimulates the body’s ability to produce insulin in response to elevated levels of blood glucose, inhibits the release of glucagon following meals, and slows food absorption. However, endogenous GLP-1 is rapidly inactivated by the peptide, dipeptidyl peptidase 4 (DPP-4).

Several synthetic GLP-1 analogues are in clinical development designed to have extended duration of action.

**REFERENCES**


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of action. Synthetic exendin-4 is likely to be the first of this new class to reach market. Exendin-4 is a hormone taken from the gila monster lizard and behaves in the same way as human GLP-1, but is much more potent and long-lasting.

Exendin-4 is currently in phase III clinical development, but early results suggest that it is effective at lowering HbA1c with a reduced risk of hypoglycaemia (Buse et al, 2004). A drawback appears to be that this class of drugs needs to be injected twice-daily.

**DPP-4 inhibitors**

This class of drugs works by inhibiting the enzyme DPP-4, which normally inactivates endogenous GLP-1. By blocking the DPP-4 enzyme, levels of GLP-1 are increased and this leads to increased insulin secretion and decreased production of glucose by the liver. A molecule called LAF237 is the most advanced of this class and is expected to enter phase III clinical trials in 2005. A major advantage is that these drugs are available as oral tablets.

**PPAR receptors**

The discovery that glitazones work by activating the peroxisome proliferator-activated receptor (PPAR) [gamma] has prompted research into other molecules targeting this receptor. Research is focused on dual-acting molecules that target PPAR [gamma] and PPAR [alpha]. The dual action of these molecules enables them to reduce blood glucose concentrations while also targeting the underlying metabolic syndrome. The first of these drugs is expected to be available in 2007, but there have been concerns over the possible serious risk of oedema and heart failure. This has prompted research into targeting the PPAR [delta] receptor, which may have less risk of adverse events.

**Non-injection insulin administration**

Although insulin tablets would be the most convenient for patients, the difficulty is that insulin is quickly broken down by digestive enzymes. Numerous methods have been tried to prevent this breakdown of insulin, such as the use of enzyme inhibitors and molecular modifications to insulin. So far investigational oral insulin formulations are ineffective at reducing blood glucose in patients. Transdermal insulin delivery using patches has also been unsuccessful to date. Short-acting, inhaled insulin formulations have met with more success. Results from phase III clinical trials with insulin administered by the dry-powder inhaler system Exubera indicate the inhaled insulin formulation given before meals is as effective as mealtime insulin injections (Quattrin et al, 2004). Exubera was filed for approval to the EMEA in March 2004. Another dry powder insulin formulation uses large porous particles loaded with insulin that are stable at room temperature — allowing the use of smaller inhalers. This system is in phase II clinical trials and results indicate similar efficacy compared with mealtime injections (Heinemann et al, 2004). Another inhaled insulin product, preliminarily known as NN1998, is administered in aerosol form via the inhaler Afrez system (Kapitza et al, 2004). Phase II trials indicate it is as effective as meal-time insulin injections and it is currently in phase III clinical development.

**Stem cell research**

The ultimate treatment for diabetes would be to give patients a new pancreas or replace their β-cells. The area that has created most research interest is the cultivation and implantation of embryonic stem cells into the pancreas to develop into insulin-producing β-cells. The problem is that the implanted cells are destroyed by the body’s immune system. Although a promising research area, its clinical availability remains some distance away.

**Advances in diabetes devices**

Computerised SMBG meters are available that allow the patient to record accurate FBG concentrations and also to save individual readings so that FBG can be monitored over a period of time to form a glycaemic control ‘diary’. Insulin pens were developed in the 1980s, but were only included on the NHS prescription list in 2000. Insulin pens have continued to be adapted and improved over the past 20 years. Modern pens offer patients an accurate, convenient and discreet method for administering their insulin. Research into insulin pen devices is ongoing and new devices will undoubtedly continue to enter the market.

Continuous subcutaneous insulin injection (CSII) via implantable insulin pumps remains the ‘gold standard’ of achieving glycaemic control, as they offer the most physiological method of delivering insulin. However, insulin pumps are prohibitively expensive for use in all patients. In addition, they are not appropriate in all cases because they require significant amounts of patient education and training (Rosenstock, 2001). NICE recommends that insulin pumps only be used in type 1 diabetes and in cases where patients cannot be treated satisfactorily with insulin injections.

**Conclusions**

The increased investment in new treatments for diabetes is a positive trend that is set to continue and will help us, as health care professionals, to achieve the best standards of care and outcomes for our patients.

References