New hypoglycaemic therapies

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Background

Therapeutic options for the treatment of diabetes were for many years limited to diet, metformin, sulphonylureas and insulin. In the 1990s, a number of new agents became available, with many others in development. At the same time, a new impetus towards improved glucose control was provided by the results of the Diabetes Control and Complications trial in type 1 diabetes and of the UK Prospective Diabetes Study in type 2 diabetes. Both studies showed clear benefits from more aggressive treatment of blood glucose. In the aftermath of these studies insulin monotherapy remains the treatment of choice for type 1 diabetes, but treatment of type 2 diabetes now aims for tight control of hyperglycaemia, hyperlipidaemia and other elements of cardiovascular risk in addition to improved blood glucose control. A typical patient with actively treated type 2 diabetes may, for example, be using insulin, metformin, a statin, an angiotensin-converting enzyme inhibitor and aspirin in addition to anti-anginal therapy. Polypharmacy means that issues such as compliance and possible drug interactions become increasingly important.

New therapies for type 1 diabetes

Type 1 diabetes causes pancreatic beta cell failure, and treatment is by hormone replacement. The principle is simple, but in practice it is extremely difficult to imitate the physiological pattern of insulin secretion. The most successful means of doing this — other than by insulin infusion pump therapy — is to inject a quick acting insulin before each main meal, with bedtime insulin to cover basal insulin requirements during the night. New short-acting insulin analogues have been introduced to provide better meal-time insulin replacement, and long-acting analogues will soon be available to cover the overnight period.

Short-acting insulin analogues

Two preparations are now available: insulin lispro and insulin aspart. Lispro is prepared by reversal of proline and lysine on positions 27 and 28 of the insulin B chain, and aspart by substitution of aspartate for proline on position B28. These analogues have receptor binding characteristics similar to human insulin, but dissociate more rapidly from hexameric configuration following injection. Peak action is reached within 30–45 minutes compared with 60–90 minutes with standard soluble insulin preparations. More rapid absorption means shorter duration of action, so comparisons with standard insulin preparations have tended to show lower postprandial but higher pre-prandial glucose levels, with little or no change in glycated haemoglobin (HbA1c).

Marketing claims that these insulins ‘can be injected immediately before meals’ and ‘are more convenient’ should be considered critically. Optimal matching of meals and insulin is achieved if the analogues are given 15–20 minutes before meals, rather than immediately before. Equally, blinded comparisons have shown that HbA1c levels are unaffected if soluble insulin is substituted for a rapid acting analogue injected shortly before a meal. Patients who want the convenience of pre-meal injection will, in general, achieve the same HbA1c if they inject their usual insulin before eating.

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In the absence of evidence that any systematic benefit is achieved by simple substitution of one insulin for another, the new insulins are best considered as precision tools to be used in the context of an intensified therapy regimen. Rather unexpectedly, however, reduced frequency of hypoglycaemia at night has emerged as a benefit of the rapid acting analogues. The relative reduction in severe or symptomatic hypoglycaemia, estimated at about 30%, is thought to be due to reduced carry-over from standard soluble insulins injected in the course of the day – an effect clearly underestimated in the past. At present, many diabetologists in the UK restrict use of rapid acting insulin analogues to selected patients on intensified insulin regimens and to those with troublesome nocturnal hypoglycaemia. Introduction of better basal insulin preparations could, however, greatly increase the scope and uptake of these analogues.

**Long-acting insulin analogues**

Current intensified insulin regimens rely on injection of intermediate-acting insulins, usually given at bedtime. These have two main disadvantages. First, insulin levels climb to a peak during the night – typically at the time of maximal diurnal insulin sensitivity – and decay towards morning. This produces a blood glucose trough in the middle of the night and a sharp rise towards morning. Secondly, variable absorption of insulin produces wide and baffling fluctuations in fasting glucose levels. There is, therefore, a strong clinical need for insulins with a flatter profile and a more predictable pattern of action.

Two long-acting analogues are currently in development:

- **Insulin glargine** (the name is a contraction of glycine/di-arginine) is produced by addition of two arginine residues to the B chain. This changes the isoelectric point of the molecule in solution, which means that the insulin is soluble at pH 4 in the vial, but forms a slowly dissolving microprecipitate at the subcutaneous site following injection. The limited evidence available to date suggests that substitution of insulin glargine for isophane insulin at night does not improve HbA1c levels, but some studies have shown a small reduction in fasting blood glucose levels and reduced nocturnal hypoglycaemia.

- A different retarding principle has been used for another insulin in development, known as NN304 (Novo-Nordisk). In this case, a short fatty acyl chain has been attached to the B29 amino acid of the insulin B chain. The effect of this modification is to promote binding to albumin in the tissues and in the circulation, thus prolonging the action profile of the insulin. Pharmacokinetic studies are promising, but few clinical studies have been reported to date.

**New therapies for type 2 diabetes**

**Diet**

Type 2 diabetes is associated with obesity, within the context of a background population that eats too much and takes too little exercise. There is a common view that diet is an ineffective form of treatment, but the problem is one of compliance rather than efficacy. Reduced calorie intake greatly improves insulin sensitivity and glucose control. Diet, exercise and weight loss remain the most effective treatments for obese type 2 diabetics with endogenous insulin secretion. Sadly, few patients achieve useful weight loss, but it should not be forgotten that therapies to enhance insulin secretion or insulin action are effectively surrogates for the only treatment regimen that truly strikes at the roots of the disease.

**Glimepiride**

Glimepiride is a sulphonylurea which is new to the UK, but it has been used in other countries and appears to have a good safety profile. Like other agents in this class, its action is mediated by closure of the potassium-adenosine triphosphate (K-ATP) channel in the beta cell membrane, which results in membrane depolarisation, calcium influx and insulin release. Glimepiride is a potent agent, with a half-life of 9–10 hours and metabolites that retain some of its activity. It is considered to carry a low risk of hypoglycaemia and to have less interaction with cardiovascular K-ATP channels than other sulphonylureas, but these potential advantages have yet to be fully substantiated. Its main practical benefit is once-daily administration. Compliance is increasingly recognised as a major issue in type 2 diabetes where polypharmacy is unavoidable, and once-daily regimens are therefore to be preferred whenever possible. It should, however, not be forgotten that gliben-
Clam and gliclazide are both effective for once-daily administration at the lower end of the dosage range.

**Repaglinide**

Repaglinide is the first of a new class of insulin secretagogues known as the meglinitides. Meglitinide itself is the non-sulphonylurea moiety of glibenclamide. As with the sulphonylureas, these agents act via closure of the K-ATP channel in the beta cells, although their receptor binding characteristics are different. Repaglinide has a plasma half-life of about one hour and is largely excreted in the bile. Taken before meals, it restores towards normal the sluggish and impaired insulin response to meals seen in type 2 diabetes. Its short duration of action is expected to reduce the frequency of hypoglycaemia. This suggestion is supported by in vitro studies indicating that – unlike sulphonylureas – repaglinide does not enhance basal insulin secretion in the absence of glucose. At present, there seems to be little consensus as to the role of prandial glucose regulation in the management of type 2 diabetes.

**Enzyme inhibitors**

The enzyme inhibitors are the rich man’s tapeworm. Acarbose and miglitol act by inhibition of alpha-glucosidase enzymes resident in the brush border of the intestinal lumen. These enzymes are responsible for breakdown of oligosaccharides into monosaccharides, and inhibition therefore results in reduced absorption of monosaccharides from the small intestine. One consequence of incomplete carbohydrate digestion in the upper bowel is that bacterial fermentation may occur in the lower bowel with socially inconvenient results. For this reason, careful titration of dose is essential but, correctly used, these agents improve postprandial glucose control and can lower HbA1c by perhaps 0.5%. Acarbose is poorly absorbed from the gut lumen, and the safety profile appears good, although raised transaminase levels and (very rarely) jaundice or hepatitis may occur.

Lipase inhibitors have been advocated for weight reduction. Orlistat inhibits fat absorption to a maximum of about 30%. Dietary adherence is critical to the success of this agent, and failure to follow a low-fat diet will lead to steatorrhoea. Some have suggested that orlistat is useful mainly because of this antibuse-like effect upon fat consumption. At present, it is not clear what role it has in diabetes management.

**Thiazolidinediones**

The glitazones, as they are often called for convenience, are a class of drugs that represent a new therapeutic principle for the treatment of diabetes. Their action, which is not well understood, is mediated by activation of the nuclear receptor, the peroxisome proliferator-activated receptor-gamma, and increased synthesis of proteins involved in the tissue effects of insulin. The effect is to reduce hepatic glucose output and to promote peripheral glucose uptake in synergy with insulin. The effect on hepatic glucose production is synergistic with that of metformin, another drug whose action is poorly understood. The glitazones reduce intra-abdominal fat deposition, a pattern associated with insulin resistance, but appear also to promote peripheral fat deposition. Weight gain is therefore a potential concern.

Use of troglitazone, the first agent in this class, has been restricted by its
hepatotoxicity. This response is idiosyncratic and infrequent, but cannot be fully avoided by repeated measurement of liver function tests, and irreversible liver failure may result. The newer agents rosiglitazone and pioglitazone appear to be safer in this respect, but two episodes of reversible liver toxicity have now been reported in patients on rosiglitazone. All three agents are currently available in the USA but not in most other parts of the world.

As monotherapy, the glitazones compare with, but are not superior to, the sulphonylureas or metformin. They may have special advantages in combination with other oral agents and insulin, particularly in patients with syndrome X (type 2 diabetes, hypertension, hyperlipidaemia, ischaemic heart disease and obesity in association with insulin resistance). Evaluation of these agents is currently hampered by lack of good controlled clinical studies; 'head-to-head' comparisons with metformin in combination therapy would be particularly useful.

Insulin treatment of type 2 diabetes

Type 2 diabetes is a progressive disorder. In its early stages, insulin secretion is increased but is insufficient to normalise glucose levels. Later in the disease process, insulin secretion begins to fail and glucose levels drift further out of control. At this stage, insulin secretagogues become ineffective (secondary failure), and insulin replacement is needed. Unnecessary delay in starting insulin was (and still is) the commonest error in diabetes management. Current practice is to consider insulin at an earlier stage – for example, when HbA1c levels exceed 8% – and many physicians now combine a single injection of NPH insulin at night with metformin during the day. This is at least as effective as twice-daily injection of pre-mixed insulin combinations. Weight gain on insulin remains a problem, especially for those who are already overweight and those for whom compliance with diet is difficult. The role of insulin analogues in type 2 diabetes remains uncertain, and the priority must surely be to make more effective use of the preparations already available.

New therapies – what is the evidence?

A literature search will generate hundreds of references for each of the new therapies mentioned in this article, but almost all the clinical studies listed were undertaken for regulatory purposes and are therefore of limited value for clinical practice. As a result, and despite the huge investment in these agents, the evidence base for their use remains inadequate. A new generation of comparative clinical studies, preferably clinician-led, will be needed before they can be introduced into evidence-based clinical practice.

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