Insulin Secretagogues

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Keywords: Hypoglycaemia – Insulin secretagogues – Nateglinide – Oral hypoglycaemic agents – Repaglinide – Type 2 diabetes mellitus

Introduction

Type 2 diabetes is one of the most common chronic diseases in the world. There is an ongoing pandemic with the number of cases of type 2 diabetes rising, in the UK alone, from 1.4 million in 1994 to 2.9 million in the year 20101.

The pathogenesis of type 2 diabetes is complex, but insulin resistance and β-cell dysfunction are both central components, although the relative contribution of these factors may vary between populations2,3. Oral agents to lower glucose in type 2 diabetes mainly target insulin resistance (metformin or thiazolidinediones) or β-cell dysfunction (insulin secretagogues). Until recently, only the sulphonylureas and metformin, a biguanide, both of which were developed in the 1950s, were routinely available.

Sulphonylureas (SU) have been the mainstay of treatment for type 2 diabetes and remain the most commonly prescribed first-line oral hypoglycaemic agent (OHA). They are insulin secretagogues and bind to a sulphonylurea receptor on the β-cell. This leads to depolarization of the β-cell membrane and stimulation of insulin. Both chlorpropamide (a first-generation sulphonylurea) and glibenclamide and gliclazide (second generation SUs) have good efficacy and outcome data. In the UKPDS, there was a signifi-
cant reduction in glycated haemoglobin (HbA1c) and reduction in risk of microvascular complications in people with type 2 diabetes with intensive therapy which included the use of sulphonylurea therapy.4

However, all SUs tend to have a prolonged binding time to the β-cell and therefore cause prolonged insulin secretion. This results in two very important problems: an increase risk of hypoglycaemia and subsequent weight gain. These are seen as major barriers to patients optimizing their glycaemic control. The United Kingdom Prospective Diabetes Study (UKPDS) was indeed a landmark study. It confirmed, at last, the belief that good glycaemic control was important in people with type 2 diabetes and improved outcome, particularly from reduced risk from microvascular complications.4 For every 1% reduction in HbA1c, there was a 21% reduction in diabetes-related deaths, a 37% reduction in microvascular disease, a 14% reduction in myocardial infarction and a 21% reduction in diabetes-related endpoints.

Although the UKPDS finally convinced us that glycaemic control is important in determining outcome in people with type 2 diabetes, it also unfortunately highlighted the shortcomings of the available glucose-lowering therapies (metformin, SU and insulin). The use of an intensive treatment regime achieved a median HbA1c which was above the normal range (normal range up to 6.2%) and increased relentlessly with time. Median HbA1c values for successive 5-year periods of follow-up in the intensively treated group were 6.6%, 7.5% and 8.1% respectively. This was achieved along with significant weight gain and increased risk of hypoglycaemia compared to the conventionally treated group. The UKPDS also revealed how ineffective the current hypoglycaemic therapies are in maintaining long-term glycaemic control when used as monotherapy.5 At 3 years into the study, half of the patients required combination therapy, and by 9 years 75% of patients required combination therapy.

The need for new, novel and durable glucose-lowering therapies is therefore clear. In this review, I will consider the new insulin secretagogues, which have recently become available for routine clinical use.

Why Target the β-Cell?

It is often thought that insulin resistance is central to type 2 diabetes. Whilst it is undoubtedly an important factor, an objective look at the evidence reveals that β-cell dysfunction plays a key role in both type 2 diabetes and ‘pre-diabetic’ states, such as impaired glucose tolerance (IGT) (Figure 1). In terms of the natural progression of type 2 diabetes, with the observation that the HbA1c rises relentlessly with time, the UKPDS confirmed that this was due to deterioration in β-cell dysfunction, whilst insulin resistance remained essentially unchanged. This progressive failure of the β-cells occurred regardless of whether patients were obese or non-obese, and also was not dependent on the mode of action of the OHA (metformin or SU) used.

The UKPDS showed that, even at the time of diagnosis, people with type 2 diabetes had only 60% of their predicted β-cell function as measured by the HOMA analysis. This fell to 25% after 6 years. Extrapolation of this data from the UKPDS means that we can calculate that β-cell dysfunction

**Figure 1.** β-Cell dysfunction: present early in disease process. Loss of early phase insulin release in subjects with IGT.
commences some 12 years before the clinical diagnosis of diabetes is made (Figure 2).

\[\text{Figure 2. UKPDS – extrapolation of the time of deterioration of } \beta\text{-cell dysfunction. Adapted from UKPDS 16, Diabetes 1995;44:1249–58}\]

\[\text{Figure 3. Insulin deficiency in type 2 diabetes. From Temple RC et al. Lancet 1989;1:293–5, reproduced with permission}\]

\[\text{β-Cell function can be considered in terms of quantity, quality and timing of insulin secretion. Quality refers to the fact that until very recently most insulin assays were unable to distinguish between insulin and its largely biologically inactive precursor molecule proinsulin}^7. \text{This has lead to many studies relatively overestimating insulin concentrations in subjects with or without diabetes}^8\.

\[\text{The development of a specific two-site immunoradiometric assay for insulin has solved this problem, and studies have shown that if these assays are used in subjects with type 2 diabetes, they have in fact lower post-challenge insulin levels}^9,10 \text{ (Figure 3). These studies also showed that subjects with type 2 diabetes have an elevated concentration of proinsulin and also its split products, 32/33 and 65/66 split proinsulin}^9,10\.

\[\text{It is not only the absolute level of insulin secreted that is important. We know that insulin release following an acute secretagogue challenge occurs as a rapid early-phase response that peaks at 2–4 min, and is over by 10 min post-challenge. There is a late (or second) phase response, which lasts for 2–3 h. The early-phase insulin response is vital for ensuring normal glucose tolerance. The early-phase insulin release also primes the tissues sensitive to it, particularly the liver, and leads to a reduction in hepatic glucose production}^{11}\.

\[\text{There is evidence that in the Caucasian population, early-phase insulin response is already lost in subjects with impaired glucose tolerance}^{12} \text{ (Figure 1). Even in populations who are classically ‘insulin resistant’ such as the Pima Indians, it is the reduction in early-phase insulin response which is the most reliable predictor of subsequent development of type 2 diabetes}^{13}.\]
Studies have shown that this diminished early-phase insulin release is associated with reduced suppression of hepatic glucose output and therefore post-challenge hyperglycaemia and also late hyperinsulinaemia\textsuperscript{14}. Undoubtedly, by the time subjects have established type 2 diabetes, the early-phase insulin release is lost and subjects exhibit both fasting hyperglycaemia as well as post-challenge or post-prandial hyperglycaemia\textsuperscript{15}.

Emerging Importance of Post-challenge or Post-prandial Hyperglycaemia

The main cause of increased mortality in subjects with type 2 diabetes is macrovascular disease, mainly myocardial infarction and stroke. Traditionally, the association between hyperglycaemia and macrovascular complications has focused on fasting glucose levels. On a practical level, monitoring of people with type 2 diabetes is focused on pre-prandial testing of glucose and recently there is a move in diagnostic testing for diabetes away from a post-glucose challenge test (the oral glucose tolerance test (OGTT)) to exclusive use of fasting glucose\textsuperscript{16}. The DECODE study (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) is the most recent and largest study to look at the relationship between fasting and post-challenge glucose (2 h glucose after a 75 g OGTT) on mortality and morbidity\textsuperscript{21} . Data in more than 25 000 subjects showed that in terms of predicting risk of mortality, post-challenge glucose was better and more sensitive than fasting glucose\textsuperscript{21} (Figure 4). This data is consistent with that obtained from other groups and in different populations\textsuperscript{22–24}.

There is a good theoretical basis of the pathogenic effect of post-prandial hyperglycaemia. Post-prandial hyperglycaemia is associated with increased production of free radicals, leading to oxidative stress\textsuperscript{25}. Endothelial dysfunction and damage is associated with post-prandial hypoglycaemia via mechanisms implicated in the athrogenic process\textsuperscript{26}. Control of post-prandial glucose is therefore an emerging target for new therapies. It offers a prospect of not only improving ‘total’ glycaemic control but also the potential, although unproven, of improving cardiovascular outcome.

New Insulin Secretagogues

Repaglinide

Repaglinide, an oral insulin secretagogue, was the first prandial glucose regulator (PGR) to be licensed and
has been available since 1998. It differs structurally from SUs as it is a carbamoylmethyl benzoic acid derivative. It is structurally related to meglitinide27,28 (Figure 5). Repaglinide binds to the sulphonylurea receptor and to its own distinct binding site on the pancreatic β-cell27. Like the sulphonylureas, repaglinide acts primarily in provoking closure of the ATP-sensitive potassium channels, which results in the depolarization of the cell membrane, an influx of calcium ions and subsequent insulin secretion.

However, in contrast to the sulphonylureas, repaglinide does not stimulate exocytosis independently of its effect on the ATP sensitive potassium channels, and insulin biosynthesis is not impaired28. Its key features are its very rapid onset of action and short duration of action. Peak repaglinide concentrations in the blood occur an hour after oral intake, and plasma levels decrease rapidly within a half-life of approximately 1 hour. These features have lead to the concept of prandial glucose regulation, with the drug being taken just before a meal28.

Clinical trials with repaglinide have shown that it is an effective hypoglycaemic compound. In patients with type 2 diabetes on diet only, the addition of repaglinide resulted in a 2.1% reduction in HbA1c, a fall in fasting glucose of 3.9 mmol/l and a fall in post-prandial glucose of 6.2 mmol/l29.

Repaglinide is metabolized by the liver into inactive substances which are then excreted, mostly via bile, with only 6% being excreted by the kidneys making it an option for those with renal impairment30. A study which compared repaglinide to the sulphonylurea glibenclamide over 12 months and including completed data on 320 subjects, showed that repaglinide was equivalent in terms of its efficacy and safety when used in a fixed-dose regime31.

Repaglinide has been used in combination with metformin in a study involving 83 subjects with type 2 diabetes, who had inadequate glycaemic control. The patients were randomized to continue with metformin alone, with metformin with the addition of repaglinide, or to receive repaglinide alone. In subjects receiving combined therapy with metformin and repaglinide, there was a significant reduction in HbA1c of 1.4% and a fall in fasting plasma glucose of 2.2 mmol/l. In the combination group, there was a 3 kg gain in weight. In this study, combined metformin and repaglinide therapy resulted in superior glycaemic control when compared to either therapy alone. Repaglinide monotherapy was as effective as metformin monotherapy32.

Sulphonylureas, because of their potential risk of hypoglycaemia, have to be used in conjunction with a regimented dosage and dietary regime. Thus patients are advised to have snacks between main meals, and that missing or delaying a meal can lead to hypoglycaemia. Because of its action as a prandial glucose regulator, one could envisage that there are potential benefits from using a drug such as repaglinide in a flexible dosing regime. Depending on the patient’s meal pattern, the patient may administer repaglinide prior to meals, usually ‘meals’ may be taken 2 to 4 times a day. The agent is taken up to 15 min before each meal. When used in this way, studies have shown that repaglinide has a significantly lower risk of hypoglycaemia compared to the sulphonylureas (including glibenclamide, gliclazide and glipizide33. A shorter-term study with repaglinide looking at the effect of missing a meal showed a significantly lower risk of hypoglycaemia compared to glibenclamide34.

Recent data in a large cohort of patients with type 2 diabetes has emphasized the practical advantages of using repaglinide in a flexible dosing regime. In this real life study over 5000 patients with type 2 diabetes who were switched from sulphonylurea to repaglinide, either as monotherapy or in combination with metformin showed significant reduction in HbA1c of around 1%, a significant fall in both fasting and post-prandial glucose measures, a fall in body weight of approximately 1.2 kg and an improvement.
in quality of life. In particular, patients appeared to find it very convenient to be able to postpone, or to skip/miss a meal.

At the present time, repaglinide is being used as a monotherapy in patients with type 2 diabetes, in whom glycaemic control is not optimal on diet only. There is good evidence of its use in combination with metformin. The recommended starting dose is 0.5 mg given just before meals (up to 15 min before) with titration of the dose up to a maximum of 4 mg q.d.s.

There is interesting data for the use of repaglinide in combination with insulin therapy. The use of oral glycaemic agents in combination with insulin is an area in which there has been interest for some time. There is good evidence of the potential advantages in both improved glycaemic control and lower dose of insulin required with the use of the combination of insulin with metformin. In terms of the combination of sulphonylurea and insulin, a large meta-analysis showed that there was some clinical advantage in using a combination of insulin with sulphonylurea in terms of improved glycaemic control. However, sulphonylureas with their prolonged hyperinsulinaemia and increased risk of hypoglycaemia are not the ideal oral agents to use in combination with insulin therapy. There is some early data looking at the use of repaglinide in combination with bedtime NPH insulin which showed an additional lowering HbA1c of 1.68% over a 14-week period in patients treated with repaglinide and combination with bedtime insulin compared to bedtime insulin alone. Further data on 45 subjects comparing twice daily soluble and isophane insulin and metformin, compared to bedtime isophane and metformin, and to bedtime isophane insulin, metformin and pre-meal repaglinide showed that in the repaglinide group the HbA1c reduction was clinically significant and comparable to the use of twice daily insulin and metformin but the insulin dose was significantly lower in the repaglinide group. These early data offer a potential for the use of prandial glucose regulators in combination with bedtime insulin and certainly appear to offer an alternative approach to management when patients with type 2 diabetes are transferring from oral hypoglycaemic agents to insulin therapy.

**Nateglinide**

Nateglinide is the second prandial glucose regulator available for clinical use. It is a completely novel agent as it is an amino acid (D-phenylalanine derivative) and has no sulphonylurea moiety (Figure 5). Nateglinide, again, elicits a rapid-onset and short-duration rise in insulin level by inhibiting pancreatic β-cell potassium ATP sensitive channels.

However, there appears to be significant differences in the kinetics of the nateglinide interaction with the β-cell potassium ATP channel in that the half-life of nateglinide binding to the receptor is a matter of seconds, compared to minutes, for instance, even with repaglinide. Nateglinide appears to have a faster onset and shorter duration of action than other insulin secretagogues including repaglinide. In comparative animal and human studies of nateglinide and repaglinide, nateglinide resulted in a faster increase in plasma insulin levels but less prolonged hyperinsulinaemia following a meal and, theoretically therefore, less risk of hypoglycaemia.

Another interesting aspect of nateglinide therapy appears to be a synergistic effect of nateglinide and meal administration on insulin secretion. This was demonstrated in 24 patients with type 2 diabetes who were given two doses of nateglinide three times daily for 7 days, with washout intervals between treatment periods. Significantly greater insulin secretion was observed when nateglinide was taken before a meal compared to nateglinide given in the fasting state.

Compared to sulphonylureas, in a double-blind placebo-controlled parallel group study of 8 weeks’ duration comparing use of nateglinide 120 mg before meals to glibenclamide, in 152 patients with type 2 diabetes, nateglinide primarily reduced the post-mealtime glucose excursions more effectively than glibenclamide, whereas glibenclamide primarily reduced fasting glucose levels. In terms of insulin secretion, nateglinide produces a more ‘physiological’ insulin release than glibenclamide, with better peak insulin levels with meals and less hyperinsulinaemia between meals (Figure 6). In subjects with type 2 diabetes, nateglinide monotherapy for 12 weeks achieved a dose-dependent reduction in HbA1c and a very low risk of hypoglycaemia. In combination with metformin, in a randomized double-blind study, patients with sub-optimal glycaemic control received either nateglinide monotherapy (n = 179 subjects), metformin monotherapy (n = 178 subjects), combination therapy (n = 172 subjects), or placebo (n = 172 subjects). Nateglinide and metformin monotherapy each improved overall glycaemic control. With nateglinide there was greater reduction in mealtime glucose following a ‘sustacal’ challenge. With metformin monotherapy there was a significant fall in fasting plasma glucose. In combination therapy there was a significant fall in HbA1c of 1.4% and a fall in fasting plasma glucose of 2.4 mmol/l.

In this study, there appeared to be more effective lowering of HbA1c in patients on nateglinide who previously had been therapy naive and also in patients who had HbA1c levels >9.5%. The most significant finding of this study was that there was no significant change.
from baseline in terms of body weight in any of the active treatment group. In the nateglinide monotherapy group the change from baseline was less than 1 kg. As this was a 6-month study, this finding appears to be in contrast to weight changes reported with other insulin secretagogues, particularly sulphonylurea in whom weight gain is an inevitable consequence.

Summary

Type 2 diabetes is a progressive and chronic disorder, which is becoming increasingly common across the world. Recent large outcome studies have emphasized both the need to improve glycaemic control in order to improve outcomes, particularly from microvascular disease, but have also vividly demonstrated the inability of existing therapy, i.e. biguanides, sulphonylureas and insulin, to maintain long-term optimal glycaemic control. The pathophysiology of type 2 diabetes is now more clearly understood, with both insulin resistance and β-cell dysfunction playing a key role. However, the UKPDS has revealed that the progressive nature of type 2 diabetes is explained by a progressive deterioration in β-cell function. Loss of early-phase insulin release, a key factor in β-cell dysfunction, is lost early in type 2 diabetes and in some populations is already lost prior to the development of type 2 diabetes. Extrapolation from the UKPDS data reveals that the deterioration of β-cell function occurs some 12 years prior to diagnosis. Existing oral insulin secretagogues, sulphonylureas, are associated with hyperinsulinaemia, risk of hypoglycaemia and weight gain. Furthermore, they are not able to offer durable glycaemic control in patients with type 2 diabetes and are associated with progressive decline of β-cell function. New insulin secretagogues offer an exciting opportunity. Repaglinide, the first prandial glucose regulator, now has convincing data that, compared to sulphonylurea use, it has a lower risk of hypoglycaemia. When used in a flexible dosing regime in a large cohort of patients, it is associated with better glycaemic control, a reduction in HbA1c, weight loss and improved quality of life compared to sulphonylureas. Early data shows the possibility of an effective combination with night time isophane insulin with potentially significant falls in HbA1c and lower doses of insulin required. Nateglinide is an amino acid derivative. It again acts directly on the pancreatic β-cell. Because of its very short duration of action, and the fact that it appears to secrete insulin in a glucose-dependent manner, it appears to secrete insulin in the closest way to that seen in a normality. Early data, both in monotherapy and in combination with metformin, show that it is an effective agent in terms of lowering HbA1c, has a low risk of hypoglycaemia and potentially less risk of significant weight gain. These characteristics mean that it may be the ideal agent to be used very early in the disease process, or even in subjects with impaired glucose tolerance, in whom early-phase insulin response is already lost. However these concepts, at the present time, are unproven.

There is increasing data linking post-challenge and post-prandial glucose to increasing risk of cardiovascular disease. Prandial glucose regulators offer the possibility of selectively targeting post-prandial glucose levels and, in theory, could potentially reduce the risk of cardiovascular disease. However, this concept is completely unproven and needs to be the subject of outcome studies. If outcome studies are able to demonstrate the prandial glucose regulators are either able to prevent the onset of type 2 diabetes in subjects with impaired glucose tolerance, or reduce the risk of cardiovascular disease, either in type 2 diabetes...
subjects or subjects with impaired glucose tolerance, then they are likely to become the first-line agent in these situations.

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