Assessing the potential for α-glucosidase inhibitors in prediabetic states

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Abstract

Type 2 diabetes often has an insidious onset with hyperglycaemia being present for many years before diagnosis is made. It is a progressive disease, due in part to loss of β-cell function, with the reduction in function probably commencing 10–12 years prior to diagnosis and being aggravated by increasing fasting plasma glucose levels. Earlier intervention in those at risk from type 2 diabetes, aimed at minimizing hyperglycaemia, may prevent or delay overt diabetes and the associated development of micro- and macrovascular disease. Six-year follow-up data from the UK Prospective Diabetes Study, confirm that sulphonylurea, metformin and insulin therapy can reduce hyperglycaemia in individuals with type 2 diabetes. Although none of these agents prevent the subsequent progressive increase in fasting glucose levels, preliminary results with acarbose show that fasting plasma glucose levels can be maintained over 1 year of therapy. Three large-scale studies are currently investigating whether treatment with acarbose at an earlier stage of the disease process, in subjects with varying degrees of glucose intolerance, may be beneficial in helping to prevent or delay the onset of diabetes. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Type 2 diabetes is often unrecognized, with hyperglycaemia being present for many years until diabetic symptoms develop or health checks reveal raised plasma glucose levels. Once diagnosed, management of type 2 diabetes can be difficult, as near normal glucose levels are usually unachievable, can rarely be maintained [1] and long-term complications, particularly macrovascular disease, pose particular problems. Coronary heart disease has been shown to be more prevalent in people with impaired glucose tolerance (IGT) than in people with normal glucose tolerance, although it is unclear whether this increased risk is hyperglycaemia-related or whether some underlying defect is responsible for both the hyperglycaemia and the cardiovascular disease [2–4]. Earlier intervention in those at risk from type 2 diabetes may be advisable to prevent or delay overt diabetes and, hopefully, prevent the development of cardiovascular complications.
Dietary intervention in IGT subjects, by means of carbohydrate restriction, in the Bedford [5] and Whitehall [6] studies showed no effect on the progression to diabetes, although limited success was seen with diet and exercise in the Malmö study [7], when analysed by actual therapy. Ericsson [7] and Bourn [8] report significant improvements in clinical and metabolic variables with a diet and exercise intervention programme in IGT subjects, but the absence of a parallel, randomized control group precludes firm conclusions. The Malmöhus study [9] showed that 23 male IGT subjects who were randomized to the sulphonylurea tolbutamide and continued to take it, did not develop diabetes over a 10-year follow-up period. One-year data from the Fasting Hyperglycaemia Study shows no glycaemic change with reinforced healthy living advice [10], but improved glycaemic control with the sulphonylurea gliclazide, although this is at the expense of weight gain and an increased risk of hypoglycaemia [11]. By contrast, the Da Qing study [12] showed a significant reduction in the proportion of IGT subjects developing type 2 diabetes when allocated to diet and exercise regimens. This 6-year Chinese study of 577 subjects in 35 clinics, showed that the incidence of diabetes per 100 person years was 15.7% for patients in the control (no intervention) group compared with 8.3–10% for subjects in the other three groups. These results suggest that enhanced dietary and exercise regimens may be effective in preventing disease progression in some populations, although their effects did not appear to be additive (diet 10%, exercise 8.3%, diet plus exercise 9.6%).

2. UK Prospective Diabetes Study

Diabetes, once established, is a chronic progressive disorder requiring lifelong therapy both for the disease itself and its complications. The UK Prospective Diabetes Study (UKPDS) [13], a randomized controlled trial of 5102 patients with type 2 diabetes, is assessing whether improved glycaemic control can reduce diabetes-related morbidity and mortality, and aims to determine if treatment with sulphonylurea, metformin or insulin can confer particular advantages or disadvantages. The UKPDS commenced in 1977 and will report in 1998. Interim analyses have shown that pharmacological intervention with chlorpropamide, glibenclamide, metformin or insulin can substantially reduce fasting plasma glucose levels when first prescribed, but over 6 years, a steady increase is seen in fasting plasma glucose levels with all therapies (Fig. 1). Homoeostasis model assessment (HOMA) [14] of fasting glucose and insulin values indicates that this progressive glucose rise is secondary to declining $\beta$-cell function [1] rather than increasing insulin resistance (Fig. 2). The rate of decline of $\beta$-cell function did not differ with diet, sulphonylurea or metformin therapy, suggesting that none of these therapies
Acarbose, a pseudo-oligosaccharide, is a competitive α-glucosidase enzyme inhibitor which diminishes postprandial blood glucose excursions by delaying carbohydrate digestion in the small intestine. In diabetic subjects, acarbose has been demonstrated to improve blood glucose control with no increased risk of hypoglycaemia or change in body weight [15]. The glycaemic efficacy of acarbose and the prevalence of side-effects show a clear dose dependency. The most common side-effect is flatulence, which occurs in 20–30% of subjects, but diminishes with continued use. Abdominal distension and diarrhoea are reported less frequently. These gastrointestinal effects can be minimized by commencing treatment at a low dose and increasing the amount taken slowly as tolerance develops.

A double-blind, randomized trial of acarbose was added to the UKPDS in 1994, using a factorial design to evaluate its potential glycaemic effects. The 1946 patients enrolled were allocated either to acarbose (n = 973), titrated to 100 mg t.i.d., or to placebo (n = 973) in addition to their existing therapy for diabetes. Preliminary results indicate that, after 1 year, fasting plasma glucose levels are maintained in patients receiving acarbose, whereas they continue to rise in those receiving placebo (Fig. 4) [16]. Three-year data are awaited to see if acarbose is able to halt the progressive increase in fasting plasma glucose levels seen with the other therapies evaluated.

Acarbose, an established treatment for type 2 diabetes, offers several advantages as a candidate for a long-term diabetes prevention therapy given that it has no major or life-threatening side-effects.
and it does not induce hypoglycaemia. A short-term pilot study in 18 subjects with IGT has shown that acarbose can reduce postprandial glucose and insulin levels with a significant increase in insulin sensitivity [17]. In this study, patients were randomized to receive acarbose or placebo for 16 weeks. Acarbose therapy decreased 2-h plasma glucose and plasma insulin levels and increased insulin sensitivity. Three large-scale studies are currently investigating whether the effects of acarbose therapy can benefit prediabetic subjects by delaying or preventing progression to diabetes.

4. The Early Diabetes Intervention Trial

The Early Diabetes Intervention Trial (EDIT), which started in 1994, is a prospective, randomized, double-blind, placebo-controlled, nine-centre, 3-year study in 631 subjects thought to be at risk of developing diabetes [18]. The primary aim of the study is to determine whether deterioration in glycaemic tolerance towards diabetes can be delayed or prevented in self-referred subjects with two consecutive fasting plasma glucose levels in the range 5.5–7.7 mmol/l, by antihyperglycaemic treatment intervention using an a-glucosidase inhibitor (acarbose) or a biguanide (metformin), alone or in combination. Three-year follow-up data on the rate of progression to type 2 diabetes, as assessed by twin oral glucose tolerance tests (OGTTs), changes in insulin sensitivity, alterations in β-cell function, prevalence of diabetic retinopathy, levels of microalbuminuria and digital electrocardiographic abnormalities will be available in 1999.

5. The Dutch Acarbose Intervention Study in IGT

The Dutch Acarbose Intervention Study in IGT (DAISI) is investigating the impact of acarbose on progression to type 2 diabetes in 163 subjects found to have IGT on two successive OGTTs. Following an active run-in period on acarbose, subjects were randomized to receive acarbose, 50 mg t.i.d., or placebo and are being followed for 3 years. The primary endpoint of this study is the proportion of subjects who develop type 2 diabetes, as confirmed by twin OGTTs. The results will be available in 1999.

6. STOP-NIDDM

The STOP-NIDDM study is a large international study involving centres in Canada, Germany, Israel, Scandinavia and Spain. It aims to recruit 1200 subjects who have IGT according to a single OGTT and have a fasting plasma glucose level ≥ 5.6 mmol/l. Eligible subjects are randomized to receive acarbose, 100 mg t.i.d., or placebo for 3 years. Prevention of progression to type 2 diabetes, as assessed by an OGTT, is the primary endpoint of this study. Secondary endpoints include the effects of acarbose on blood pressure, cardiovascular events, glucose tolerance, insulin sensitivity, hyperinsulinaemia, lipid profiles and anthropometric profiles.

7. Conclusions

Early intervention in subjects at increased risk of developing type 2 diabetes may be beneficial in delaying or preventing the onset of the disease. In addition, prevention of hyperglycaemia could reduce the risk of macro- and microvascular complications. Intensive lifestyle interventions, involving diet and exercise, may be able to pre-
vent the progression to diabetes from varying degrees of glucose intolerance, but are unlikely to be practical, especially in populations with a westernized lifestyle. Pharmacological interventions may therefore be appropriate.

Results to date suggest that agents, such as sulphonylureas and metformin, although highly effective for reducing plasma glucose levels, are unable to halt the progressive increase in fasting plasma glucose levels, or the accompanying decrease in β-cell function. Preliminary UKPDS results suggest that the addition of acarbose therapy to pharmacological intervention with chlorpropamide, glibenclamide, metformin or insulin can halt the progressive rise in fasting plasma glucose levels over 1 year. Three-year data are awaited to see if this effect is maintained in the longer term. The degree to which early intervention with acarbose can prevent or delay progression to diabetes is likely to be clarified in the next 2–3 years with the analysis of results from the EDIT, DAISI and STOP-NIDDM trials.

References