The thiazolidinediones: a new class of antidiabetic agents

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Insulin resistance is a fundamental feature of type 2 diabetes and is strongly associated with metabolic disorders which predict increased cardiovascular risk, including hypertension and dyslipidaemia. A new class of insulin-sensitizing agents, the thiazolidinediones, reduce insulin resistance and improve glycaemia both as monotherapy and in combination with sulphonylureas or metformin.

Type 2 diabetes mellitus is a common, serious and progressive disease, imposing heavy burdens of morbidity and premature mortality. In the UK, more than 95 000 people are diagnosed with this condition each year — a new case every 5 minutes. According to British Diabetic Association (BDA, 1996) figures, between 1 035 000 and 1 242 000 UK adults have type 2 diabetes. Since there is generally acknowledged to be one undiagnosed case for each diagnosed, a total of at least two million people in the UK are thought to have type 2 diabetes. Sedentary lifestyles and an ageing, increasingly obese population do not suggest an early fall in the high incidence of this common metabolic disorder (BDA, 1996; Budd, 1998).

Coronary artery disease and stroke are easily the most frequent causes of death in people with type 2 diabetes. The incidence of these vascular events is about 2–4-fold higher than in non-diabetic populations. Coronary heart disease is the main cause of death in over 50% and cerebrovascular disease in 15% of people with this condition (Kings Fund Policy Institute, 1996). Furthermore, cardiovascular disease is frequently present at first diagnosis of type 2 diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), 16% of men and 23% of women had abnormal electrocardiographic findings at diagnosis. In a World Health Organization study of vascular disease in diabetic men, 45% of subjects showed evidence of macrovascular disease after 8 years of follow-up and 43% had ischaemic heart disease (Kings Fund Policy Institute, 1996).

VASCULAR COMPLICATIONS AND INSULIN RESISTANCE

The true burden of type 2 diabetes has been clarified by the recently completed CODE-2 (the Costs of Diabetes in Europe-Type 2) study, a coordinated investigation into type 2 diabetes management in eight European countries (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the UK).

The initial results, presented at the 1999 European Association for the Study of Diabetes (EASD) meeting (unpublished data, EASD, 1999), showed that 5% of health-care budgets are consumed by the care of type 2 diabetes. The largest proportion of this cost was for hospital care of diabetic complications. The management of either macrovascular complications (myocardial infarction, angina, stroke, leg amputation, heart failure and coronary artery bypass graft) or microvascular complications (foot ulcer, blindness in one or both eyes, photocoagulation, vitrectomy, dialysis and renal transplantation) doubled the average cost per patient. The presence of both types of complications increased costs 3.5-fold. The CODE-2 results reinforce the need for effective therapy to delay progression of disease and reduce the incidence of cardiovascular complications.

It is now widely acknowledged that insulin resistance is a fundamental cause of type 2 diabetes. In non-diabetic individuals, insulin resistance in combination with hyperinsulinaemia has a strong predictive value for the future development of type 2 diabetes. Moreover, insulin resistance is strongly associated with metabolic disorders which predict increased cardiovascular risk, including hypertension, dyslipidaemia (especially high triglyceride and low high density lipoprotein levels), impaired glucose tolerance, microalbuminuria and coronary heart disease (collectively referred to as the insulin resistance syndrome, IRS) (Haffner and Miettinen, 1997).

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COMPLICATIONS AND CURRENT THERAPY

The UKPDS showed that microvascular complications (retinopathy, neuropathy and nephropathy) can be reduced by intensive management of blood glucose. However, the study also highlighted several limitations of current therapy: although early reductions in glycaemic levels were achieved, these were not sustained and many patients required up to three oral agents to maintain long-term blood glucose control.

Furthermore, the antidiabetic agents used in UKPDS did not significantly reduce the macrovascular complications of type 2 diabetes, despite maintaining a 0.9% difference in glycosylated haemoglobin (HbA1c) between the conventionally and intensively treated groups (UKPDS Group, 1998). This failure to significantly reduce cardiovascular events suggests that other factors, such as insulin resistance, could be playing a role in their pathogenesis.

Current antidiabetic agents include sulphonylureas, biguanides, alpha-glucosidase inhibitors and insulin treatment. Sulphonylureas stimulate secretion of insulin from functioning pancreatic beta cells: treatment achieves traditional glycaemic targets in about 60–70% of patients. The drawbacks of sulphonylureas include secondary failure (lack of efficacy with time because of gradual pancreatic beta cell failure), weight gain and induction of hyperinsulinaemia which can lead to hypoglycaemia.

The biguanide metformin lowers blood glucose by effects which include inhibiting hepatic glucose production. Gastrointestinal side-effects such as heartburn, diarrhoea and anorexia are common. The alpha-glucosidase inhibitors, when taken with a meal, reduce the postprandial glucose peaks by retarding glucose uptake from the intestines. Gastrointestinal side-effects such as flatulence, diarrhoea and abdominal bloating commonly occur. Type 2 patients who are not adequately controlled by diet and/or oral hypoglycaemic agents may be treated using insulin in monotherapy or combined with sulphonylureas or metformin. Hypoglycaemia is uncommon with once-daily long-acting insulin but increases predictably with intensified insulin regimens (Williams, 1994). In addition, weight gain may be a problem. Despite this, insulin remains a very important treatment for those type 2 patients inadequately controlled on oral agents.

One new class of oral agent for type 2 diabetes — the thiazolidinediones (TZDs) or 'glitazones' — looks promising.

THIAZOLIDINEDIONES

The TZDs or glitazones are a new class of oral antidiabetic agent specifically designed to target insulin resistance, a fundamental feature of type 2 diabetes. TZDs, such as rosiglitazone and pioglitazone, enhance sensitivity to insulin in the liver, adipose tissue and muscle, resulting in improved insulin-mediated glucose disposal. TZDs are also known as peroxisome proliferator-activated receptor (PPAR) gamma agonists, because one of their key actions is to activate the nuclear receptor PPAR gamma. This receptor, which is expressed at high levels in mammalian adipose tissue, regulates the transcription of several genes involved in preadipocyte differentiation and insulin-mediated glucose uptake in peripheral tissues (Barman Balfour and Plosker, 1999).

Thus, unlike conventional sulphonylurea agents, the PPAR gamma agonists act by improving insulin sensitivity (relieving insulin resistance) rather than by increasing insulin secretion. In animal models of insulin resistance, PPAR gamma agonists decreased plasma glucose, insulin and triglyceride levels and also attenuated or prevented diabetic nephropathy and pancreatic islet cell degeneration.

In clinical trials in patients with type 2 diabetes these agents have improved glycaemic control, as shown by decreases in fasting plasma glucose and HbA1c. Consistent with their mechanism of action, PPAR gamma therapy is associated with a very low risk of hypoglycaemia. Furthermore, and of potential great importance, addition of a PPAR gamma agonist to existing sulphonylurea, metformin or insulin therapy achieves further reductions in fasting plasma glucose and HbAlc (Barman Balfour and Plosker, 1999).

RECENT RESULTS

Promising data on PPAR gamma agonist therapy were presented at the recent EASD meeting. Data presented show that the PPAR gamma agonist, rosiglitazone, decreases insulin resistance and improves beta-cell function when used as monotherapy or in combination with other oral hypoglycaemic agents such as metformin or sulphonylureas (Matthews et al, 1999).

Rosiglitazone monotherapy appears to be an effective alternative to sulphonylureas as first-line therapy for type 2 diabetes with a lower risk of hypoglycaemia (Lonnqvist et al, 1999; Owen et al, 1999). In a comparative 12-month trial, rosiglitazone was at least as effective as glibenclamide in reducing fasting plasma glucose.

Fifty one per cent of patients taking rosiglitazone achieved a target fasting plasma glucose of less than 7.8 mmol/litre compared with 37% of glibenclamide-treated patients. Symptoms which could relate to hypoglycaemia were reported in 12% of the glibenclamide-treated patients compared with only 1% of rosiglitazone-treated patients. Glycaemic control was maintained with rosiglitazone over 12 months, whereas glibenclamide treatment appeared to be associated with a gradual loss of effect over time (Lonnqvist et al, 1999).

In a series of combination studies, addition of rosiglitazone to either sulphonylureas or metformin was effective and well-tolerated, with a good safety profile and tolerability comparable to placebo (Fonseca et al, 1999; Gomis et al, 1999; Kreider, 1999). In these combination studies, rosiglitazone provided significantly superior glycaemic control to that achieved with sulphonylurea or metformin monotherapy. Treatment was also effective in patients aged over 65 years, with a good safety profile and tolerability similar to placebo (Kreider, 1999), an important consideration given the high proportion of type 2 patients in this age group.

Other data showed that this agent produced significant reductions in plasma insulin concentrations, urinary albumin excretion, triglycerides in patients in whom these were elevated, and levels of circulating free fatty acids (Budd, 1998; Bakris et al, 1999; Jones et al, 1999; Lonnqvist et al, 1999; Tabona et al, 1999). Elevation of high-density lipoprotein (HDL) levels with improvement or no change in total cholesterol to HDL ratio was also reported (Goldstein and Salzman, 1999).

The use of another PPAR gamma agonist, pioglitazone, was also reported at the EASD. Pioglitazone significantly reduces levels of HbAlc, fasting blood glucose and triglycerides while increasing levels of HDL. Total and low-density lipoprotein cholesterol levels were not significantly different from placebo (Mathisen et al, 1999).

SAFETY OF PPAR GAMMA AGONISTS

The withdrawal from the UK of troglitazone, the prototype TZD, following a small number of cases of idiosyncratic hepatotoxicity, spurred close monitoring of newer entrants such as rosiglitazone and pioglitazone. Safety data for rosiglitazone presented at the EASD were reassuring with no sign of hepatotoxicity (Salzman and Patel, 1999). Pooled data from 4500 patients taking rosiglitazone (alone or with other oral hypoglycaemic agents) showed that the proportion of rosiglitazone-treated patients with elevated alanine transaminase levels (greater than 3 times the upper limit of reference range) was similar to the proportions of patients treated with placebo or active comparators.

Modifications to the side chains of TZDs are believed to account for differences in metabolism, activity and toxic effects. It is currently thought that the hepatotoxicity associated with troglitazone may be related to its alpha-tocopherol moiety — a molecular configuration which is not shared by rosiglitazone or pioglitazone. Troglitazone also produces a quinone metabolite, and induces CYP3A4, features which have been associated with liver toxicity in other classes of agents.

At therapeutic doses, rosiglitazone does not inhibit any of the major cytochrome P450 enzymes and has been shown to have no effect on the pharmacokinetics of a number of other drugs metabolized by CYP3A4, including nifedipine and oral contraceptives. Therefore, concomitant therapy with rosiglitazone and drugs metabolized via cytochrome P450 is unlikely to lead to clinically important drug interactions, an important consideration because patients with type 2 diabetes frequently receive multiple concurrent medications (Thompson et al, 1999). Data on pioglitazone similarly showed no inhibition of cytochrome P450 enzymes and no drug interaction with several drugs used commonly in diabetic patients (Kortboyer and Eckland, 1999).

Generally speaking, PPAR gamma agonists are well tolerated with safety profiles similar to placebo.

Adverse events which are probably class effects include weight gain, small reductions in haemoglobin and haematocrit (as a result of haemodilution), increased plasma volume and oedema. The average weight gain observed is modest — in the order of 2–3 kg — and does not seem to have a significant metabolic impact.

These class effects are unlikely to present problems for the majority of patients.

CONCLUSIONS

Recent data on TZDs are encouraging and support a role for this class of agents in the treatment of type 2 diabetes. The potential, for the first time, to effectively target insulin resistance offers a new therapeutic tool. If this action translates into an impact on the costly vascular complications of type 2 diabetes, these agents will be particularly valuable additions to our current armamentarium. HM

Conflict of interest: Professor Barnett has given advice on thiazolidinediones to Glaxo Wellcome and SmithKline Beecham. He has lectured at symposia supported by them and has received research funding from them in studies of their products.

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KEY POINTS

- Type 2 diabetes is a major public health problem imposing a substantial burden on the individual, and on the health service.
- Insulin resistance is a key underlying metabolic abnormality in most patients with type 2 diabetes.
- Current therapies for type 2 diabetes do not target insulin resistance.
- A new class of agent, thiazolidinediones, improve insulin resistance.
- These agents, used alone or in combination with existing therapies, may help reduce the burden of type 2 diabetes.