REVIEW ARTICLE

Drugs 2000 Nov; 60 (5): 1017-1028
0012-6667/00/0011-1017/$25.00/0

Antidiabetic Drugs Present and Future:
Will Improving Insulin Resistance Benefit Cardiovascular Risk in Type 2 Diabetes Mellitus?

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Abstract

Results from the United Kingdom Prospective Diabetes Study showed that intensive treatment of type 2 (non-insulin–dependent) diabetes mellitus, with sulphonylureas or insulin, significantly reduced microvascular complications but did not have a significant effect on macrovascular complications after 10 years. Insulin resistance plays a key role in type 2 diabetes mellitus and is linked to a cluster of cardiovascular risk factors. Optimal treatment for type 2 diabetes mellitus should aim to improve insulin resistance and the associated cardiovascular risk factors in addition to achieving glycaemic control. Treatment with sulphonylureas or exogenous insulin improves glycaemic control by increasing insulin supplies rather than reducing insulin resistance. Metformin and the recently in-

troduced thiazolidinediones have beneficial effects on reducing insulin resistance as well as providing glycaemic control. There is evidence that, like metformin, thiazolidinediones also improve cardiovascular risk factors such as dyslipidaemia and fibrinolysis. Whether these differences will translate into clinical benefit remains to be seen. The thiazolidinediones rosiglitazone and pioglitazone have been available in the US since 1999 (with pioglitazone also being available in Japan). Both products are now available to physicians in Europe.

Type 2 (non-insulin–dependent) diabetes mellitus results from a combination of tissue resistance (or insensitivity) to insulin action and an inadequate compensatory insulin secretory response.[1] Both genetic and environmental factors probably contribute to the development of this form of diabetes mellitus although the specific causes are not yet understood. Most patients with type 2 diabetes mellitus are obese, and obesity itself results in insulin resistance. Insulin resistance is a condition in which peripheral tissues (adipose tissue and skeletal muscle) show reduced sensitivity to the effects of insulin-stimulated glucose uptake and this leads to hyperglycaemia. Peripheral insulin resistance is considered to have a key role in the development of type 2 diabetes mellitus; it is also closely linked to many other risk factors for cardiovascular disease: hypertension, left ventricular hypertrophy, sedentary lifestyle, upper body obesity, impaired fibrinolysis and atherogenic dyslipidaemia. All these conditions are independently linked with progressive atherosclerosis and cardiovascular events.

1. Current Management Recommendations

The current recommendations of the American Diabetes Association, for the care of patients with diabetes mellitus, advocate reduction of blood glucose as the goal of treatment.[1] These recommendations are based on the principle that blood glucose should be lowered to, or near to, normal levels in all patients. They are supported by evidence that tight glycaemic control reduces the risk of microvascular diabetic complications. This evidence comes from trials in patients with both type 1 (insulin-dependent)[2,3] and type 2 diabetes mellitus.[4,5] Such trials commonly use glycosylated haemoglobin (HbA_{1c}) levels, which reflect the state of glycaemia over the preceding 8 to 10 weeks, as an indicator of glycaemic control.

In the Diabetes Control and Complications Trial, intensive insulin therapy was found to delay the onset and slow the progression of diabetic retinopathy, nephropathy and neuropathy in patients with type 1 diabetes mellitus (n = 1441) roughly half of whom had mild retinopathy at baseline.[2] Mean HbA_{1c} levels were maintained at around 7% throughout the study in the intensively treated group compared with around 9% in those given conventional therapy (after the first year). Similarly, in the Stockholm Diabetes Intervention Study in 102 patients with type 1 diabetes mellitus and unsatisfactory blood glucose control, nephropathy, neuropathy and nonproliferative retinopathy (including serious retinopathy) were all significantly retarded in the group given intensified insulin treatment.[3] Those given intensive insulin treatment for 7.5 years showed greater improvement in glucose control than those given standard treatment. Mean HbA_{1c} levels were reduced from 9.5 to 7.1% on intensive treatment and from 9.4 to 8.5% on standard treatment.

Intensive blood glucose control with chlorpropamide, glibenclamide or insulin substantially decreased the risk of microvascular complications compared with conventional treatment in 3867 patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study (UKPDS).[5] Mean HbA_{1c} levels over the 10 years were 7.0% in the intensively treated group and 7.9% in the conventional dietary treatment group. The Kumamoto study of patients with type 2 diabetes (n = 110) also showed that there were significant reductions in the onset and progression of nephropathy, retinopathy and neuropathy after 6 years of intensive insulin

treatment compared with conventional treatment.[4] Mean HbA_{1c} levels in the two treatment groups were similar to those reported in the Diabetes Control and Complications Trial after a few months of the study.

These studies were consistent in demonstrating that tight glycaemic control reduces the risk of microvascular disease. The effects of tight glycaemic control on macrovascular disease, however, were not clear from these studies, either because this issue was not addressed or because, as in the case of the UKPDS,[5] tight glycaemic control did not have a significant effect on the risk of macrovascular disease (after more than 10 years of follow-up). The influence of treatments on macrovascular disease is particularly important: although 9% of patients with type 2 disease develop a microvascular complication within 9 years of diagnosis, 20% have a macrovascular complication. Furthermore, macrovascular disease is 70-fold more likely to result in death than a microvascular complication in these patients.[6] Normalisation of blood glucose levels may be achieved either by increasing insulin levels (with sulphonylureas to increase endogenous insulin secretion or with exogenous insulin) or by improving insulin sensitivity (metformin, thiazolidinediones).

2. Negative Aspects of Hyperinsulinaemia

Although *in vitro* and animal experimental data have suggested that insulin may promote atherosclerosis, however, there are no but human data to support this finding. Moreover, insulin treatment in patients with type 2 diabetes mellitus and intensive insulin treatment in patients with type 1 diabetes mellitus has not been associated with an increased rate of microvascular complications. High insulin levels are assumed to represent insulin resistance in epidemiological studies and their results cannot be interpreted as necessarily indicating a harmful effect of insulin itself. However, the use of agents, such as sulphonylureas or insulin, which promote hyperinsulinaemia may have some adverse effects.

Data from animal and *in vitro* experiments and from epidemiological studies suggest that insulin or insulin resistance may have a direct role in the development of atherosclerosis. Long term treatment with insulin results in lipid-containing lesions and thickening of the arterial wall in experimental animals. Insulin also inhibits the regression of diet-induced experimental atherosclerosis, and insulin deficiency inhibits the development of arterial lesions. Insulin stimulates lipid synthesis in arterial tissue and this effect of insulin is influenced by haemodynamic factors and may be localised in certain parts of the artery. Physiological insulin levels stimulate proliferation and migration of cultured arterial smooth muscle cells but have no effect on endothelial cells cultured from large vessels. Insulin also stimulates cholesterol synthesis and low density lipoprotein (LDL) cholesterol binding in both arterial smooth muscle cells and monocyte macrophages.[7] Elevated insulin levels increase the level of circulating plasminogen activator inhibitor 1 (PAI-1) in an environment of increased glucose and triglycerides, typical of type 2 diabetes mellitus.[8] Increased levels of PAI-1 can lead to decreased fibinolytic activity which, in turn, may predispose to thrombosis.

In addition to this evidence from experimental studies, evidence from epidemiological studies in men without diabetes mellitus suggests a link between plasma insulin levels and ischaemic heart disease. The Quebec Cardiovascular study in men without diabetes mellitus was undertaken to determine whether plasma insulin levels were independently related to ischaemic heart disease after adjustment for other risk factors including plasma lipoprotein levels.[9] Blood samples were collected from 2103 men without ischaemic heart disease aged 45 to 76 years. A first ischaemic event, (angina pectoris, acute myocardial infarction or death from ischaemic heart disease) occurred in 114 of the men during the next 5 years (case patients). Each of these men was matched with a control who had remained free of ischaemic heart disease and fasting plasma insulin levels at baseline were 18% higher in patients than in controls. The association

between plasma insulin levels and ischaemic heart disease remained after adjustment for other cardiovascular risk factors such as high systolic blood pressure, use of medication, family history of ischaemic heart disease, high plasma levels of triglycerides, apolipoprotein B, high density lipoprotein (HDL) and LDL cholesterol. Deprés et al.[9] concluded that high fasting plasma insulin levels appear to be independently related to ischaemic heart disease in men.

The British Regional Heart study examined this question using a similar approach.[10] Insulin levels were determined in nonfasting serum samples from 5550 men (aged 40 to 59 years) without known diabetes mellitus. After 11.5 years of follow-up, 521 major ischaemic heart disease events had occurred, 261 fatal and 260 nonfatal. There was a nonlinear relationship between serum insulin levels and ischaemic heart disease events, the risk increasing greatly at the highest insulin levels (33.8 mU/L or more). There was some attenuation of the relationship when adjustments were made for a range of ischaemic heart disease risk factors but the relationship remained significant even after the adjustments. The data were consistent with the view that a high level of serum insulin is atherogenic with a threshold effect.

There is considerable evidence of a relationship between raised serum insulin levels and ischaemic heart disease but the nature of that relationship is not yet clear. Elevated plasma insulin levels may only be a marker for common aetiological factors in the development of both ischaemic heart disease and type 2 diabetes mellitus. The UKPDS[5] results did not indicate an increased cardiovascular risk from the use of exogenous insulin or sulphonylureas, but neither was there a significant reduction in risk. It seems possible that some of the therapeutic benefits of using these agents may be offset by the potential detrimental impact of increased circulating insulin levels on cardiovascular outcomes. In view of these doubts it may be wiser to avoid hyperinsulinaemia by favouring treatments that reduce insulin resistance over treatments, such as sulphonylureas or exogenous insulin, which are likely to produce hyperinsulinaemia.

3. Sulphonylureas

3.1 Mode of Action

Sulphonylureas exert hypoglycaemic action mainly by stimulating insulin release both in the basal state and in response to glucose load.[11] This mechanism requires functional pancreatic β-cells. Sulphonylureas interact with specific receptors at the plasma membrane of the insulin-releasing pancreatic β-cells where they inhibit adenosine triphosphate (ATP)-sensitive K^+ channels resulting in depolarisation of the cell membrane, opening of voltage-sensitive Ca^{2+} channels, increase in intracellular calcium levels and subsequent insulin release. Thus, endogenous insulin secretion is stimulated but insulin synthesis is unaffected. This effect of sulphonylureas is augmented by glucose; further the sensitivity of β-cells to glucose and nonglucose stimuli is increased. Extrapancreatic effects of the sulphonylureas include promotion of better insulin sensitivity and insulin receptor binding, although these effects may well be secondary to improvement of hyperglycaemia. The idiopathic loss of first-phase insulin release in type 2 diabetes mellitus is not restored by sulphonylureas but second-phase insulin production is stimulated (by up to about 25%) in a dose-dependent manner in healthy individuals.[11] Insulin production is only stimulated by sulphonylureas if there is a sufficient mass of β-cells. Reductions in the available β-cells with progression of type 2 diabetes mellitus results in inadequately stimulated insulin release. There may be parallel reductions in hepatic insulin clearance and pancreatic glucagon release although this latter effect has been questioned.[11]

3.2 Favourable Effects

The sulphonylurea compounds are effective in reducing blood glucose levels in patients with type 2 diabetes mellitus and are commonly used when conventional dietary treatment fails to normalise blood glucose levels.[5,12,13] After 3 to 6 months of treatment with sulphonylureas basal and postprandial plasma glucose levels decrease by roughly 3 to 5 mmol/L, HbA_{1c} levels decrease by about 20%

and basal and postprandial insulin levels increase by about 50%.[14] In the UKPDS the sulphonylureas chlorpropamide and glibenclamide were both more effective than conventional dietary treatment in reducing HbA_{1c} levels in patients with type 2 diabetes mellitus. Median HbA_{1c} levels over 10 years were 6.7% with chlorpropamide and 6.7% with glibenclamide compared with 7.1% with insulin and 7.9% with conventional dietary treatment.[5] In general the efficacy of individual sulphonylureas does not differ greatly.

The UKPDS[5] found that intensive treatment with chlorpropamide, glibenclamide or insulin produced a 25% reduction in the risk of microvascular end-points, including the need for photocoagulation, compared with conventional dietary treatment. There was no difference between the 3 agents in the effect produced.[5] Small, short term studies with gliclazide show no apparent effect on nephropathy or retinopathy but there are some reports that gliclazide may delay the progression of diabetic retinopathy more than other sulphonylureas.[14,15] There is evidence, mainly from animal studies, that gliclazide may inhibit thrombus formation, improve fibrinolytic activity, reduce platelet hyperadhesiveness and inhibit abnormal platelet aggregation and release.[15] However, whether glycaemic control contributes to these actions, and to what extent, remains controversial.

3.3 Adverse Effects

Sulphonylureas carry a slight but recognised risk of causing acute severe hypoglycaemia, with its associated risks of death or serious neurological sequelae. The consequences of the less severe recurrent hypoglycaemia in sulphonylurea-treated patients are not established. In the UKPDS the proportion of patients experiencing major hypoglycaemic episodes per year were 0.7, 1.0, 1.4 and 1.8% with conventional dietary treatment, chlorpropamide, glibenclamide and insulin, respectively. The corresponding proportions experiencing any hypoglycaemic episode in these treatment groups were 10, 16, 21 and 28%, respectively.[16] All the sulphonylureas are reported to cause severe hypoglycaemia but drugs with longer duration of action, such as chlorpropamide and glibenclamide carry the greatest risk. This risk is further increased when drug elimination is reduced by renal impairment and it has been recommended that longer-acting sulphonylureas should be avoided in elderly patients.[17]

O'Keefe et al.[18] considered concerns about the cardiovascular safety of the sulphonylurea compounds in a recent review. Such concerns date back to the University Group Diabetes Program,[19] a prospective randomised trial that found that patients with diabetes mellitus treated with tolbutamide rather than placebo showed increased cardiovascular mortality. The significance of these findings was controversial, however, partly because of criticisms of the methods used.[18] Experimental animal data have underlined concerns about the cardiovascular safety of sulphonylureas in patients with type 2 diabetes mellitus. Sulphonylurea compounds lower blood glucose levels by blocking the opening of ATP-sensitive K^+ channels in the β-cells of the pancreas but they also block the opening of these channels in other tissues including the myocardium and this may have deleterious effects on the cardiovascular system.[18,20] Blocking the K^+ ion channels abolishes ischaemic preconditioning and increases the size of myocardial infarction in experimental animal models. Sulphonylureas are also vasoconstrictors and worsen vascular reactivity; they have been reported to increase the risk of death during long term follow-up after coronary angioplasty, and to increase the risk of in hospital mortality after angioplasty for acute myocardial infarction.[18] Finally, these compounds may increase atherogenesis and the incidence of cardiovascular events by promoting bodyweight gain and increasing plasma insulin levels.

O'Keefe et al.[18] did not reach firm conclusions about the cardiovascular safety of the sulphonylureas. Despite all of the potential adverse effects, some studies, such as the UKPDS, have not shown any increase in cardiovascular events with intensive glycaemic control using sulphonylureas. O'Keefe et al.[18] considered it prudent, however, to minimise the use of these agents and to use low doses

and shorter-acting sulphonylureas in patients with cardiovascular disease. Berger et al.[21] also reviewed the cardiovascular safety of the sulphonylureas and considered that sulphonylureas may exert cardiotoxic adverse effects in patients with ischaemic heart disease. They did not recommend the general use of sulphonylureas for patients with type 2 diabetes mellitus until the tolerablility and efficacy of these agents has been proven with regard to relevant clinical end-points.

Some sulphonylureas, such as glibenclamide, are taken up in the cells more readily and might give rise to an increased risk of cardiovascular complications.[14] Glibenclamide also has a longer lasting and irreversible effect on membrane potential. Glimepiride, a newer sulphonylurea, is a more selective potassium channel blocker which may have less negative cardiovascular effects, although this remains to be proven.[18] Animal experiments have shown marked differences between the sulphonylureas in their effects on cardiac function.[22] Glibenclamide and gliclazide, for example, produce stronger coronary vasoconstriction, and subsequent cardiac dysfunction than glimepiride in anaesthetised dogs.

4. Repaglinide

4.1 Mode of Action

Repaglinide is a novel insulin-releasing agent developed from the nonsulphonylurea portion of glibenclamide. Repaglinide is the first in the class of short-acting insulin secretagogues that work by closing ATP-dependent potassium channels. There are at least 2 repaglinide receptor binding sites on the β-cell, one of which is the sulphonylurea receptor.[23] However, although repaglinide stimulates insulin release in a similar manner to sulphonylureas, its pharmacokinetic properties confer a rapid onset and short duration of action.

4.2 Favourable Effects

Reductions in fasting blood glucose (FBG) and HbA_{1c} levels with repaglinide monotherapy are similar to those observed with sulphonylureas.[24] Because of its short duration of action (1 to 2 hours) repaglinide only stimulates insulin secretion to cover the postprandial period without causing sustained insulin release between meals. It can therefore be omitted if the meal is missed ('skip-a-meal'). Furthermore, the glucose-lowering effect of repaglinide is additive to that of metformin.[25]

4.3 Adverse Effects

Hypoglycaemia and bodyweight gain are the main adverse effects associated with repaglinide treatment. However, early evidence suggests that the risk of hypoglycaemia is about 3-fold lower with repaglinide than with sulphonylureas.[23]

Another new short-acting secretagogue, nateglinide, is also undergoing clinical trials. The use of short-acting insulin secretagogues may preserve β-cell function although this remains to be shown in clinical practice.

5. Improving Insulin Sensitivity

Since insulin resistance is a fundamental problem in type 2 diabetes mellitus, focusing on treatment to improve insulin sensitivity seems appropriate. Unlike the sulphonylureas or insulin itself, treatments that improve insulin sensitivity tend to reduce, rather than increase, circulating insulin levels. This approach may have additional beneficial effects on dyslipidaemia, hypertension and fibrinolytic activity, in addition to effects on hyperglycaemia.[18] Therapeutic options that improve insulin sensitivity include biguanides (e.g. metformin), and thiazolidinediones, which appear to specifically influence insulin sensitivity in peripheral tissue sites (e.g. skeletal muscle and adipose tissue).

5.1 Biguanides (Metformin)

5.1.1 Mode of Action

Metformin is antihyperglycaemic but not hypoglycaemic: it lowers blood glucose levels in the presence of hyperglycaemia but does not decrease them below the normal range. Metformin does not affect pancreatic insulin secretion and is not effective in the absence of insulin. The relative contribution of the various effects of metformin in achieving its antihyperglycaemic effect is controversial.

Proposed mechanisms for the antihyperglycaemic effect include enhanced insulin-stimulated glucose uptake from the blood into the tissues, decreased glucose production in the liver, and decreased intestinal absorption of glucose.[23,26] Metformin accumulates in the intestinal wall and decreases glucose absorption in animals but this mechanism alone does not account for the antihyperglycaemic effect of metformin in patients with diabetes mellitus. In addition, metformin inhibits hepatic glucose production in obese and lean patients with diabetes mellitus. There is also evidence that metformin increases glucose uptake and utilisation in adipose tissue, skeletal muscles, erythrocytes and intestines, but not in the brain, liver, skin and renal medulla.

The mechanism by which metformin improves peripheral disposal of glucose has now been linked to the activity of the drug on glucose uptake mechanisms, which are dependent of glucose transporter (GLUT) systems that differ according to tissue.[27] Metformin appears to act by facilitating the activity of glucose transporters; it does not appear to affect the subcellular distribution of the major glucose transporter in skeletal muscle, GLUT 4, (as does insulin) but stimulates the transport of GLUT 1 from the intracellular compartment to the plasma membrane. Its effect differs from that of insulin and this may account for its additive effect with other treatments which increase insulin levels, such as sulphonylureas.[27] The clinical implications of this *in vitro* effect are not yet clear.[17]

5.1.2 Favourable Effects

Metformin is considered to be a first-line treatment for glycaemic control in patients who are obese (where adequate control is not achieved with diet alone) since unlike the sulphonylureas it does not tend to promote bodyweight gain and may cause some bodyweight loss.[26,28] This approach has been underpinned by the results of the UKPDS study[16] which showed that intensive treatment with metformin caused a decrease in the risk of diabetes-related end-points in overweight patients with diabetes mellitus and was associated with less bodyweight gain and fewer hypoglycaemic attacks than were insulin and sulphonylureas.[16] The drug is also used in combination with other agents, such as sulphonylureas, and may provide satisfactory glycaemic control for several years. Dunn and Peters[28] reviewed clinical studies of metformin monotherapy in obese and non-obese patients (mainly comparisons with other agents) and metformin was associated with either no change or a reduction in bodyweight in all studies whereas sulphonylurea treatment was always associated with no change or, more commonly, an increase in bodyweight. Most investigators reported similar antihyperglycaemic efficacy for metformin and sulphonylurea treatment. Reductions in FBG and randomly determined blood glucose levels were 7 to 45% of baseline after metformin, compared with 8 to 43% after sulphonylurea treatment.

In the UKPDS,[16] 753 overweight patients with newly diagnosed type 2 diabetes mellitus who had raised fasting plasma glucose levels without hyperglycaemic symptoms after 3 months initial diet were included in a randomised controlled trial comparing conventional treatment, primarily with diet alone, with intensive blood glucose control using metformin. A secondary analysis compared the 342 patients allocated to metformin with 951 overweight patients allocated to intensive blood glucose control with sulphonylureas or insulin. In a supplementary trial, 537 overweight and non-overweight patients who were already on maximum sulphonylurea therapy but had raised fasting plasma glucose levels were allocated to continuing sulphonylurea therapy alone or to the addition of metformin. In the comparison of metformin with conventional treatment, median HbA_{1c} level was 7.4% compared with 8% in the conventional group. Those treated with metformin had risk reductions of 32% for any diabetes-related end-point, 42% for diabetes-related death and 36% for all-cause mortality. Compared with the other intensive glucose control therapies (chlorpropamide, glibenclamide or insulin), metformin showed a significantly greater effect on any diabetes-related end-point, all-cause mortality and stroke.

Metformin improves various aspects of the serum lipid profiles of patients with hyperlipidaemia; it generally decreases serum levels of triglycerides, very low density lipoproteins and LDL cholesterol, and has been found in some studies to decrease total cholesterol and slightly increase HDL cholesterol levels.[26,29-32]. In one study of patients with dyslipidaemia (fasting plasma triglycerides >2.0 mmol/L) and mild type 2 diabetes mellitus (fasting plasma glucose <7.5 mmol/L) treatment with metformin, 2.5 g/day for 3 months, had favourable effects on plasma lipoprotein levels as well as on glycaemic control. Plasma glucose, plasma insulin, free fatty acid and triglyceride levels all declined while the plasma HDL cholesterol level increased.[30] In contrast, in another study in patients with type 2 diabetes mellitus inadequately controlled by diet alone, metformin improved glycaemic control and significantly reduced the plasma LDL cholesterol levels but did not affect the serum triglyceride or HDL cholesterol levels.[33]

In addition to its favourable effects on lipid profiles, metformin is reported to have a number of other potentially beneficial vascular effects.[26,29] Decreased platelet density and aggregability and increased fibrinolytic activity have been reported after metformin treatment in clinical studies.[26,28,29] Increased fibrinolytic activity may result from an increase in tissue plasminogen activator levels and reductions in tissue plasminogen activator antigen and PAI-1 levels.[26,28,31] Blood pressure and arterial resistance may also be reduced by metformin but it is unclear whether these changes are direct effects of the drug or are the result of overall improvements in metabolic and glycaemic status.

5.1.3 Adverse Effects

Gastrointestinal adverse effects of metformin are dose related and affect an estimated 5 to 20% of patients, but are usually mild and transient. These effects include anorexia, abdominal discomfort, nausea, metallic taste in the mouth and diarrhoea.[17,28] Taking metformin with food and gradually increasing the drug dosage will usually minimise or avoid these effects. Diarrhoea may respond to dosage reduction, however, any reduction in dose may compromise glucose control and combination therapy may be required to achieve optimal glycaemic control.

Lactic acidosis is a potentially serious adverse effect associated with the use of biguanides. Metformin is thought to decrease gluconeogenesis from alanine, pyruvate and lactate, which may at times lead to accumulation of lactic acid.[28] Small increases in blood lactate levels are characteristically associated with metformin treatment. The reported prevalence of lactic acidosis with metformin ranges from 0 to 0.084 occurrences per 1000 patient-years resulting in a mortality risk of 0 to 0.024 per 1000 patient-years. A recent review of worldwide data has estimated the prevalence of this adverse effect at 0.03 cases per 1000 patient-years.[34] Some reviewers have noted that the incidence of metformin-associated lactic acidosis is significantly lower than the incidence of hypoglycaemia associated with glibenclamide and has a similar mortality rate.[28,34]

Metformin use is contraindicated in patients with renal or hepatic impairment or with alcoholism, all of which are associated with decreased lactate clearance. Conditions that promote tissue hypoxia and the subsequent accumulation of lactate, including acute cardiac failure and various forms of circulatory shock, are also contraindications to metformin treatment. Metformin may be used in elderly patients who do not have any of the above contraindications.[28]

5.2 Thiazolidinediones

The thiazolidinediones improve insulin sensitivity at peripheral tissue sites (skeletal muscle and adipose tissue) resulting in increased insulin-dependent glucose disposal.[35] Their action is dependent on the presence of endogenously produced insulin. The improved insulin sensitivity results in improved glycaemic control, as evidenced by reduced plasma glucose and HbA_{1c} levels, without increasing circulating insulin levels. The direct action of these compounds in improving insulin resistance together with their effect on some cardiovascular risk factors suggests that they may have

advantages in the treatment of type 2 diabetes mellitus.

5.2.1 Mode of Action

The mechanism of action of the thiazolidinediones at the cellular level has not been fully elucidated.[35] There is, however, a variety of experimental data suggesting that the thiazolidinediones stimulate transcriptional events in the adipocytes by activating a specific nuclear receptor, the peroxisome proliferator-activated receptor gamma (PPARγ), which is expressed mainly in white and brown adipocytes.[36] The lipophilic thiazolidinediones readily enter the cells and bind to PPARγ which results in activation of regulatory sequences of DNA that control the expression of specific genes, some of which are also controlled by insulin. Thiazolidinediones thus amplify or mimic certain genomic effects of insulin on adipocytes. The main resulting effects of thiazolidinediones on adipocytes are increased fatty acid uptake and lipogenesis. The obesity that might be expected to result has not been observed suggesting that other mechanisms counter excessive adipogenesis. There is some evidence that thiazolidinediones may cause glucose- and lipid-lowering effects in the absence of white and brown adipose tissue. It has also been suggested that these compounds may bind with lower affinity to other forms of PPARs in muscle, liver and other tissues resulting in different effects from those seen in adipose tissues.[36]

Increased expression of insulin-sensitive genes, which are activated by PPARγ are considered to be the main route through which thiazolidinediones reduce insulin resistance. The interactions of these compounds with PPARγs, however, may not fully explain their biological effects. Other explanations that have been proposed include lowering circulating triglyceride and non-esterified fatty acid levels, which will increase insulin sensitivity by correcting imbalances in the glucose–fatty acid cycle, increased GLUT production and translocation into the plasma membrane in skeletal muscle and fat, increased hepatic glucose disposal, decreased hepatic glucose production and reduction of tumour necrosis factor (TNF)-α (thus reducing local aggravation of insulin resistance induced by TNFα).[36]

5.2.2 Favourable Effects

The thiazolidinediones reduce hyperglycaemia in a range of animal models with impaired glucose tolerance and obesity/diabetes syndromes similar to type 2 diabetes mellitus.[36] The effects are dose-dependent and high dosages reinstate normal or near-normal glycaemia in less severely hyperglycaemic animal models without causing overt hypoglycaemia. Improvement in insulin sensitivity with thiazolidinediones generally involves both increased peripheral glucose disposal and reduced hepatic glucose production in models with hyperinsulinaemia.

5.2.3 Troglitazone

Troglitazone was the first thiazolidinedione to reach the market. Numerous clinical trials in both obese and non-obese patients with diabetes mellitus demonstrated the efficacy of troglitazone as monotherapy and combination therapy for lowering blood glucose levels over periods of 6 weeks to 1 year.[35] Due to hepatotoxicity issues (see section 5.2.7), the drug was withdrawn from sale in all countries by March 2000.

5.2.4 Rosiglitazone

Rosiglitazone has been evaluated as monotherapy in more than 2300 patients with type 2 diabetes mellitus. Doses of 4 to 12 mg/day significantly improved glycaemic control compared with placebo. After 26 weeks of treatment, FBG and HbA_{1c} levels were reduced by about 13 to 28% and 9 to 17%, respectively, compared with placebo (table I).[37] The addition of rosiglitazone 2 to 8 mg/day, given once or twice daily, to pre-existing sulphonylurea, metformin or insulin therapy resulted in further reductions in fasting plasma glucose and HbA_{1c} levels.[38-40] Rosiglitazone was launched in the US in 1999 and in the UK and Europe in 2000. In the US, it may be used as monotherapy or in combination with metformin or sulphonylureas but in the UK and Europe it is presently licensed for combination use with either sulphonylureas or metformin.

Table I. Comparison of the utilisation profile of thiazolidinediones currently available in the US

Drug	Indication in the US	Dosage and administration
Pioglitazone	Use as monotherapy or in combination with sulphonylureas, metformin or insulin	15-45 mg/day once daily
Rosiglitazone	Use as monotherapy or in combination with metformin, only	4-8 mg/day once or twice daily

5.2.5 Pioglitazone

Pioglitazone has been assessed in over 3500 patients with type 2 diabetes mellitus. HbA_{1c} and FBG levels were significantly decreased with pioglitazone 15 to 45mg, given once daily, compared with placebo. Reductions in FBG and HbA_{1c} levels after 26 weeks of treatment were about 15 to 25% and 9 to 16%, respectively, compared with placebo (table I). In patients naïve to oral antidiabetic therapy, pioglitazone 45 mg/day reduced HbA1c levels by 19.38% compared with baseline values. HbA_{1c} levels increased by 6.86% from baseline values in placebo recipients.[41] The addition of pioglitazone 15 to 30 mg/day to sulphonylureas, metformin or insulin therapy produced additional reductions in FBG and HbA_{1c} levels. The therapeutic effect of pioglitazone was observed in patients regardless of the dosage of pre-existing therapy.[37] Pioglitazone was launched in the US in 1999 and may be used as monotherapy or in combination with metformin, sulphonylureas and insulin. In the UK and Europe, pioglitazone is likely to become available in late 2000 for combination therapy with metformin or sulphonylureas.

5.2.6 Effects on Cardiovascular Risk Factors

Improvements in lipid profile appear to be a class effect of thiazolidinediones, however, there do appear to be some subtle differences in effects on individual lipid parameters. Studies using high dosages of troglitazone demonstrated significant reductions in serum triglyceride and non-esterified fatty acid levels.[36,42] Marked reductions in serum triglyceride levels have been observed with all dosages of pioglitazone (15 to 45 mg/day), whereas changes in serum triglyceride levels during rosiglitazone therapy were variable and not significantly different from placebo.[37] Dose-dependent reductions in serum free fatty acid levels have been observed with rosiglitazone treatment.[43] Serum HDL cholesterol levels are significantly increased with pioglitazone within the first 24 weeks of treatment, but are only slightly increased during rosiglitazone therapy. Pioglitazone shows no significant changes in serum LDL cholesterol and total cholesterol levels over placebo, whereas rosiglitazone is associated with significant increases in serum LDL cholesterol and total cholesterol levels compared with placebo.[37] The overall effect of long term treatment with thiazolidinediones on lipid metabolism and its impact on the related cardiovascular risk needs to be further investigated.

5.2.7 Adverse Effects

In worldwide clinical trials, more than 5000 patients have been treated with rosiglitazone or pioglitazone. The overall incidence and types of adverse events reported with rosiglitazone and pioglitazone therapy were not significantly different from those with placebo.[37]

Severe, and sometimes fatal, hepatotoxicity has been observed with troglitazone[36] and this led to the withdrawal of the drug from markets in the UK, Japan and the US, and to the abandonment of its approval process in Europe.

In clinical trials the incidence of liver dysfunction with rosiglitazone and pioglitazone was similar to that observed with placebo.[37,44] However, liver enzyme monitoring is recommended before initiation of therapy with either agent, and periodically thereafter. In the meantime, several thousand patients are being treated with these agents in the US with an incidence of liver dysfunction comparable to that seen in clinical trials (0.2%). Furthermore, a recent US Food and Drug Administration statement concerning the withdrawal of troglitazone in the US reported that rosiglitazone and pioglitazone offer the same benefits as troglitazone without the same risk.[45]

Increased plasma volume has been reported after administration of thiazolidinediones in healthy

individuals and these agents should not be used in patients with moderate to severe (New York Heart Association functional class III or IV) chronic heart failure.[36,46] Peripheral oedema has also been seen with thiazolidinediones and this may be due to a vasodilatory effect. Bodyweight gain (in the order of 3 to 4kg) has also been noted in the first year of treatment with thiazolidinediones. Monotherapy with thiazolidinediones has not been associated with hypoglycaemia to date.

6. Conclusion

The rationale for the use of agents such as insulin and sulphonylureas, which increase circulating insulin levels, in patients with type 2 diabetes mellitus may be questioned in light of recent evidence. There is, so far, no clear evidence that their use reduces macrovascular disease, which is the main cause of death in these patients. Use of agents such as metformin or the newer thiazolidinediones that specifically reduce insulin resistance appears to be a more logical approach to the treatment of patients with type 2 diabetes mellitus since improvement of insulin sensitivity is closely linked with a cluster of risk factors for cardiovascular disease. Thiazolidinediones offer an alternative management option for the treatment of patients with type 2 diabetes mellitus, especially where hyperinsulinaemia is present at diagnosis. These drugs may be used as monotherapy or in combination therapy. In terms of glucose-lowering efficacy, pioglitazone (30 to 45mg once daily) and rosiglitazone (4mg once to twice daily) appear to achieve similar reductions in FBG and HbA_{1c} levels as currently available oral antidiabetics. As their effect is greatest where there is still sufficient circulating insulin, they should be used as early as possible in the treatment of patients with type 2 diabetes mellitus.

In conclusion, in those patients with type 2 diabetes mellitus who are overweight, the positive cardiac benefits seen in the UKPDS would support the use of metformin as the drug of choice where diet, exercise and lifestyle measures do not achieve satisfactory glycaemic control. However, alternative therapies will be necessary where monotherapy with metformin has adverse effects, and in combination with metformin or sulphonylureas where either drug alone is insufficient for controlling blood glucose levels. The thiazolidinediones offer a new approach in the treatment of patients with type 2 diabetes mellitus through reduction of insulin resistance, improvement of glycaemic control and positive secondary benefits on β-cell function. Clinical experience with these new agents will show if their effect on lowering insulin resistance improves cardiovascular outcome. The promise is there and the clinical end-point results are awaited.

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