Pioglitazone and sulfonylureas: effectively treating type 2 diabetes

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SUMMARY

Type 2 diabetes is characterised by a gradual decline in glycaemic control and progression from oral glucose-lowering monotherapy to combination therapy and exogenous insulin therapy. Functional decline of the insulin-secreting β-cells is largely responsible for the deterioration in glycaemic control. Preservation of β-cell functionality, in addition to maintaining glycaemic control and reducing insulin resistance, is now regarded as a key target for long-term management strategies. Early, aggressive intervention with combination therapy is emerging as a valid approach to optimise long-term outcomes and combining agents with differing modes of action and secondary effect profiles should prove valuable. Sulfonylureas and thiazolidinediones exert their glucose-lowering effect through differing mechanisms of action – the sulfonylureas by stimulating insulin secretion, whereas the thiazolidinediones are insulin sensitizers. Both agents offer excellent improvements in glycaemic control when given as monotherapy or in combination. The thiazolidinediones protect β-cell structural and functional integrity and functionality and complement the sulfonylures by inducing and maintaining improvements in insulin resistance, the abnormal lipid profile associated with type 2 diabetes and other cardiovascular risk factors. Thus, there is a strong rationale to support the addition of thiazolidinediones to sulfonylures as a treatment option for type 2 diabetes. This combination may be particularly effective in the early stages of the disease when β-cell function is at its highest, allowing maximal benefit to be obtained from the insulin secretion-promoting abilities of the sulfonylures and the β-cell-protective effects of the thiazolidinediones.

Introduction

Patients with type 2 diabetes characteristically experience a gradual decline in glycaemic control and progression from oral glucose-lowering monotherapy to combination therapy and ultimately to exogenous insulin therapy (1,2). A decrease in the number of functional insulin-producing β-cells contributes to the pathological decline in glycaemic control typically seen in type 2 diabetes (3) and preserving β-cell function has emerged as a vital component of long-term management strategies.

Already at diagnosis of type 2 diabetes about 50% of insulin secretion capacity is lost (4). There is now increasing evidence available that near to normal glucose control prevents progressive deterioration of insulin secretion. Therefore, a move towards introducing combination therapy earlier in the course of type 2 diabetes with the aim of preserving glycaemic control and β-cell function and thereby improving long-term outcomes is considered as a better approach to meet the dual defect in pathophysiology of type 2 diabetes. Such an approach poses the challenge of defining optimal combination regimens and the point at which to introduce them. Recent studies suggest that early, aggressive dual or even triple combination therapy in newly diagnosed patients slows the decline in glycaemic control compared with standard monotherapies (5,6). Intervening before the onset of frank type 2 diabetes in high-risk groups, such as those with gestational onset diabetes (7,8) or individuals with impaired glucose tolerance (9,10), is also emerging as a relevant approach to reducing the long-term morbidity and mortality of this chronic disease.

Insulin resistance is a core feature of type 2 diabetes. Although not all individuals with insulin resistance will go on to develop type 2 diabetes, in those that do, overt type 2 diabetes develops when β-cells are no longer able to compensate for insulin resistance and the accompanying rise in counter-regulatory hormones (11). Insulin resistance is therefore a key target in the treatment of type 2 diabetes.

The combination of a sulfonylurea and a thiazolidinedione may be a particularly effective treatment option in the early stages of type 2 diabetes when β-cell function is at its highest. This allows maximal benefit to be obtained from the insulin secretion-promoting abilities of the sulfonylures and the β-cell-protective effects of the thiazolidinediones.
resistance. Insulin resistance in itself may contribute to the decline in β-cell function by inducing endoplasmic reticulum stress as a consequence of an increased demand for insulin (11). This is in addition to the toxic effects of elevated glucose and lipid levels because of their impaired metabolic processing in the presence of insulin resistance (12).

Today, a variety of agents of differing modes of action are available to improve glycaemic control. The sulfonylureas (e.g. glipizide, glyburide, glimepiride and gliclazide) are insulin secretagogues that act to increase insulin secretion. Biguanides (principally metformin), reduce hepatic glucose output and increase the uptake of glucose by peripheral tissues. More recently, the thiazolidinediones (pioglitazone and rosiglitazone) have emerged as novel, effective glucose-lowering agents (13). The thiazolidinediones are peroxisome proliferator-activated receptor gamma (PPARγ)-stimulating insulin sensitisers that also act without increasing insulin secretion. Other, less widely used agents include the α-glucosidase inhibitor, acarbose, the incretin mimetic, exenatide, and the new short-acting insulin secretagogues, repaglinide and nateglinide. A variety of agents with novel mechanisms of action are currently in development and their role in future management regimens has yet to be defined. All these agents have varying, primary or secondary, effects on β-cell function. Recent research effort has focused on defining the effect of oral glucose-lowering agents in this respect to guide decisions on appropriate combination therapies to achieve long-term outcomes beyond glycaemic control.

This review examines the mechanistic distinctions in terms of glycaemic control and β-cell functional preservation and the latest clinical data that support the rationale for thiazolidinedione–sulfonylurea combination therapy in patients with type 2 diabetes.

Glycaemic control

The sulfonylureas and biguanides formed the mainstay of oral glucose-lowering therapy from their introduction in the early 1940s until the 1990s when thiazolidinediones became available. Sulfonylureas stimulate endogenous insulin secretion via their action at the K<sub>ATP</sub> channel in the plasma membrane of pancreatic β-cells (14) and effectively decrease HbA<sub>1c</sub> levels by between 0.8% and 2.0% (15). As sulfonylureas act by enhancing insulin secretion, they are most effective in the early stages of type 2 diabetes when β-cell function is at its greatest. Despite their initial efficacy, glycaemic control is inevitably lost over time with the sulfonylureas, necessitating the introduction of combination therapy to regain control and prolong the time before progression to exogenous insulin therapy. In the United Kingdom Prospective Diabetes Study (UKPDS), 53% of newly diagnosed type 2 diabetics initially treated with sulfonylureas subsequently required additional treatment within 6 years to maintain glycaemic control (16). In the recently published ADOPT study, the proportion of the patients with type 2 diabetes exceeded the target fasting blood glucose level of 180 mg/dl after follow-up (17). Given the direct effects of the sulfonylureas on the β-cell and the potential for β-cell exhaustion, combination regimens with agents that improve glycaemia by different modes of action, such as the thiazolidinediones, are recommended. This combination may be particularly effective given the known positive effects of the thiazolidinediones on β-cell function discussed below.

The thiazolidinediones act as insulin-sensitising agents and increase the peripheral action of insulin. They act as ligands of PPARγ, which is involved with the regulation of genes that control glucose homeostasis and lipid metabolism and is found in high concentrations in adipose tissue, hepatocytes and skeletal muscle. These agents have also proved effective in reducing HbA<sub>1c</sub> levels and maintaining glycaemic control, with average reductions in HbA<sub>1c</sub> levels of between 0.5% and 1.5% (15,18). Recent evidence suggests that the thiazolidinediones may be more effective than sulfonylureas in maintaining glycaemic control over the long term (17,19). In a direct comparison of pioglitazone vs. gliclazide as monotherapy, significantly more pioglitazone-treated patients maintained their glycaemic control at 2 years than did patients treated with gliclazide (19).

Short- and long-term studies with thiazolidinediones and sulfonylurea in combination have shown that this combination offers sustained glycaemic control (20–27). Aljabri et al. (20) found that, compared with the addition of bedtime insulin to maximal doses of sulfonylurea or metformin, the addition of pioglitazone resulted in comparable improvements in glycaemic control and less hypoglycaemia after 16 weeks of treatment. Although this study did not report separate results for the sulfonylurea and metformin groups, there was an overall reduction in HbA<sub>1c</sub> of 1.9% compared with 2.3% for insulin (20). In another short-term study, Kipnes et al. (27) looked at the pioglitazone–sulfonylurea combination exclusively and reported decreases of 0.9% and 1.3% for pioglitazone doses of 15 and 30 mg, respectively, over 16 weeks.

Long-term studies also support the sustained beneficial effects of this combination on glycaemic control (Table 1). In a 6-month study, Comaschi et al. (23) reported significant and sustained reductions in
HbA₁c when pioglitazone was added to either sulfonylurea or metformin. Four further studies of increasing duration have also confirmed the maintenance of glycaemic control following the addition of pioglitazone to sulfonylurea therapy. In the Quartet study, the addition of pioglitazone to existing sulfonylurea therapy resulted in a 1.2% reduction in HbA₁c after 1 year in 319 patients with inadequately controlled type 2 diabetes (25). Derosa et al. (28) also reported significant (1.3%; p < 0.01 from baseline) and sustained reductions in HbA₁c levels when either rosiglitazone or pioglitazone were added to failing glimepiride in 91 patients with type 2 diabetes and the metabolic syndrome after 1 year. In the 2-year end point of the Quartet study described above, comparing the addition of pioglitazone or metformin to failing sulfonylurea therapy, found that after a rapid decrease in HbA₁c levels over the first 20 weeks of the study plateaued with overall reductions of 1.03% and 1.16% for the pioglitazone plus sulfonylurea and metformin plus sulfonylurea addition groups, respectively, after 104 weeks of treatment (21). The recently presented glycaemic results of the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study (22) of 5238 patients with type 2 diabetes and evidence of macrovascular disease further support the maintenance of glycaemic control following the addition of pioglitazone to existing sulfonylurea therapy. A subgroup analysis of the PROactive study looked at the 1001 patients who were managed with sulfonylurea therapy at baseline. Patients treated with pioglitazone experienced significant decreases from baseline in HbA₁c levels that were sustained up to the 34.5-month assessment and fewer patients switched to or required addition of metformin or insulin compared with those who received placebo [Figure 1; (22)].

### Effects of thiazolidinediones and sulfonylureas on β-cell stress

Thiazolidinediones and sulfonylureas exert opposing effects on β-cell functionality over time. β-cell stress is reduced with thiazolidinedione therapy, but enhanced with sulfonylurea therapy (29).

Studies have shown that chronic exposure to glibenclamide can lead to an acceleration of β-cell apoptosis and β-cell exhaustion or desensitisation (30–34). The precise mechanism by which glibenclamide initiates β-cell apoptosis remains unclear, but may involve closure of the inwardly rectifying K⁺ sulfonylurea receptor subtype of the ATP-sensitive

| Study                     | Comparator groups                  | N    | Duration | Glycaemic effects                                      | Lipidaemic effects                                      |
|---------------------------|-----------------------------------|------|----------|-------------------------------------------------------|--------------------------------------------------------|
| Comaschi et al., 2006 (23)| Pioglitazone + sulfonylurea       | 6 months | Significant and comparable improvements in HbA₁c at 12 months (p = 0.0001) | Significant improvement across all lipid parameters |
|                           | Pioglitazone + metformin           |      |          |                                                       | Significant decrease in triglyceride levels in the pioglitazone + sulfonylurea group only |
| Torre et al., 2006 (79)   | Pioglitazone + sulfonylurea       | 77   | 6 months | Not reported                                           | Significant improvement in HDL-cholesterol levels     |
|                           | Pioglitazone + metformin           | 103  |          |                                                       | Significant improvement across all lipid parameters   |
| Derosa et al., 2004 (85)  | Glimepiride + pioglitazone        | 45   | 1 year   | Significant and comparable improvements in HbA₁c at 12 months (p < 0.01) | Significant improvement across all lipid parameters   |
| Ginis et al., 2006 (24)   | Glimepiride + rosiglitazone       | 44   |          | Significant improvement in both groups from baseline   | Worsening of multiple lipid parameters                |
|                           | Pioglitazone + sulfonylurea       | 791  | 1 year   | Significant improvement in both groups from baseline   | Triglycerides decreased significantly in both groups (p < 0.0001) |
|                           | Pioglitazone + metformin           | 705  |          |                                                        | Overall reduction of 12.8% for both groups combined for total cholesterol |
| PROactive Charbonnel and Scheen, 2006 (22); Spanheimer et al., 2006 (78) | Pioglitazone + sulfonylurea       | 508  | 3 years  | Significantly greater improvements over time in HbA₁c vs. placebo (p < 0.001 at final visit) | Significant improvement in triglyceride and HDL-cholesterol levels vs. placebo |
|                           | Placebo + sulfonylurea             | 493  |          |                                                        |                                                        |
| Quartet Charbonnel et al., 2005 (21) | Pioglitazone + sulfonylurea       | 319  | 2 years  | HbA₁c reduced by 1.03%                                  | Significant reduction in triglycerides and greater increase in HDL-cholesterol (p < 0.001) vs. metformin + sulfonylurea |
|                           | Metformin + sulfonylurea           | 320  |          | HbA₁c reduced by 1.16%                                  |                                                        |

**Table 1 Long-term glycaemic and lipidaemic effects of combined sulfonylurea and thiazolidinedione therapy in patients with type 2 diabetes**
potassium channel (32, 34), the sustained enhancement of Ca\(^{2+}\) influx mediated by glibenclamide leading to elevated and toxic cytosolic Ca\(^{2+}\) levels (33) and nitric oxide production (30). In addition, prolonged exposure to sulfonylurea renders \(\beta\)-cells less responsive to subsequent sulfonylurea stimulation. Davalli et al. (31) found that prolonged \textit{in vitro} exposure of human pancreatic islets to various insulin secretagogues, including sulfonylureas, resulted in a reduced capacity to respond to further secretory stimulation. Interestingly, certain sulfonylureas may offer a protective effect from hydrogen peroxide-induced \(\beta\)-cell damage (35).

Several lines of evidence support the beneficial effects of thiazolidinediones in terms of improving insulin secretion, preserving \(\beta\)-cell mass and islet structure and also protecting \(\beta\)-cells from oxidative stress (36–42). How the thiazolidinediones exert these protective effects remains unclear. In the presence of chronically elevated glucose levels (glucotoxicity), elevated free fatty acid (FFA) levels (lipotoxicity) appear to play an important role in \(\beta\)-cell damage during the early stages of type 2 diabetes, impairing their functionality and inducing cell death (43, 44). In the presence of both chronic hyperglycaemia and elevated FFA levels, \(\beta\)-cells synthesise less insulin and lose the glucose-stimulated insulin secretion response (45, 46). Thiazolidinediones may protect against the toxic effects of chronically elevated lipid levels by limiting the exposure of \(\beta\)-cells to circulating FFAs (47) and by their effects on triglyceride partitioning in tissues. They may also protect against \(\beta\)-cell apoptosis and facilitate \(\beta\)-cell proliferation more directly by preventing Nuclear Factor (NF)\(\kappa\)B activation in \(\beta\)-cells (37, 48). Amyloid deposition has also been associated with increased \(\beta\)-cell apoptosis (49) and a reduction in amyloid deposition with thiazolidinediones has been demonstrated \textit{in vivo} (50). The protective effects of the thiazolidinediones in this respect may be exerted \textit{via} activation of a phosphatidylinositol 3-kinase (PI3K) Akt cascade, which acts to inhibit the human islet amyloid polypeptide (h-IAPP) induction of apoptosis (51). Recently a strong effect of pioglitazone on low-grade-inflammation in patients with cardiovascular disease (CVD) without diabetes has been described, which may be another way to protect the \(\beta\)-cells (52).

**Insulin resistance**

Clinical studies have also provided indirect support for the preservation of \(\beta\)-cell function with thiazolidinedione therapy. Homeostasis model assessment (HOMA) is a mathematical tool that models the glucose–insulin feedback loop in the homeostatic state. It permits estimations of insulin sensitivity (\%S) and \(\beta\)-cell function (\%B) from pairs of fasting glucose and insulin (or C-peptide) measurements. A 23-week study of pioglitazone monotherapy showed that there was an increase in HOMA-\%B (53). In a separate study in drug-naïve patients with type 2 diabetes, Wallace et al. (54) reported an increase in HOMA-%B during 3 months of pioglitazone therapy compared with a small decrease among patients receiving placebo. In addition, they reported a significant decrease in the pro-insulin/insulin ratio suggesting that the \(\beta\)-cells were under less stress. This observation has also been reported for rosiglitazone (55). Other studies have also reported improvements in the insulinogenic index (provides a measure of \(\beta\)-cell function during an oral glucose tolerance test) and the disposition index (in which the value is corrected for underlying insulin resistance) (56–58). These improvements in \(\beta\)-cell function appear to be maintained during long-term studies. For example, in studies comparing pioglitazone and gliclazide either as monotherapies (19) or as add-on treatments to existing therapy (59), both agents were associated with an initial improvement in the HOMA-%B. However, only patients treated with pioglitazone were able to maintain this improvement during 2 years of treatment, while those treated with gliclazide experienced a continued gradual decline, despite a greater initial improvement [Figure 2; (19, 59)].

Studies support an effect for both thiazolidinediones and sulfonylureas in improving insulin resistance in the short term in type 2 diabetes using techniques such as the hyperinsulinaemic/euglyca-
mic clamp (which allows the determination of the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycaemia) and HOMA-%S (54,60–64). However, direct comparisons during long-term treatment suggest that the thiazolidinediones may be better able to improve and maintain improvements in insulin sensitivity (19,65). During 1 year of treatment, pioglitazone therapy was associated with significant reductions in HOMA-%S (p = 0.002 from baseline), whereas no significant decrease was recorded for gliclazide in patients with type 2 diabetes (65). Similarly, in a 2-year study, Tan et al. (19) found that pioglitazone was associated with an improvement in HOMA-%S, while gliclazide was associated with a worsening in this measure of insulin resistance. Combining sulfonylurea therapy with thiazolidinediones may ensure long-term benefits in terms of insulin resistance (66).

In the ADOPT study, comparing rosiglitazone with glibenclamide and with metformin in early type 2 diabetes, rosiglitazone improved insulin resistance and β-cell function to a significantly greater extent than both competitors did (17).

**Control of dyslipidaemia and other cardiovascular risk factors**

In addition to the toxic effects of elevated FFAs on β-cells, the abnormal lipid profile – including elevated small dense LDL, lowered HDL-cholesterol and elevated triglycerides – associated with type 2 diabetes poses a further burden in terms of increasing the risk of CVD. Thus, most studies of glucose-lowering therapy now also include an assessment of lipid effects.

Older sulfonylureas appear to be associated with adverse cardiovascular risks, possibly due to their binding to ATP-sensitive potassium channels in cardiomyocytes and vascular smooth muscle cells (67,68). However, how these effects might translate into clinical implications is poorly defined and the newer sulfonylureas appear to be associated with a lower risk of adverse cardiovascular events, such as myocardial infarction and may in fact inhibit atherosclerotic plaque formation (69,70). Patients with pre-existing CVD may be particularly sensitive to the effects of sulfonylureas in this respect (71,72), as studies in which such patients were excluded showed no increased risk of cardiovascular mortality (73). No primary effects on lipid profile induced by sulfonylureas are seen.

Pioglitazone has been shown to improve the lipid profile in patients with type 2 diabetes by increasing HDL-cholesterol levels, decreasing triglyceride levels and increasing the lipoprotein particle size of LDL in combination regimens with sulfonylurea (20,27,74). Evidence is emerging of a differential effect between the thiazolidinediones in this respect (75,76). In the study reported by Peters Harmel et al. (76) described above, the addition of pioglitazone to metformin and/or sulfonylurea therapy was associated with a decrease in triglyceride levels and an increase in HDL-cholesterol levels. The addition of rosiglitazone also resulted in an increase in HDL-cholesterol, but with no significant improvement in triglyceride levels and an overall increase in total cholesterol levels (76). More recently, Khan et al. (75) reported on the improvement in lipid parameters in patients switched from rosiglitazone–sulfonylurea combination therapy to pioglitazone–sulfonylurea therapy in addition to continued stable statin therapy. After 17 weeks of treatment, replacement of rosiglitazone with pioglitazone was associated with significant improvements in triglyceride and total cholesterol levels and more modest improvements in LDL-cholesterol (75). Long-term studies have shown that the beneficial effects associated with pioglitazone therapy are maintained over months and years [Table 1; (21,24,74,77–79)].

Thiazolidinediones have other advantages over traditionally employed oral agents, including additional
potential cardioprotective effects, such as improving the pro-thrombotic state and blood pressure. When given in combination with the sulfonylurea, glimepiride, both rosiglitazone and pioglitazone have been shown to improve key components of the pro-thrombotic state associated with type 2 diabetes [including plasminogen activator inhibitor 1 levels] (28). In a study of patients with type 2 diabetes and the metabolic syndrome failing on initial therapy with a sulfonylurea or metformin, combination therapy with glimepiride and either pioglitazone or rosiglitazone was associated with significant improvements in both systolic and diastolic blood pressure over 12 months (80). In addition, thiazolidinediones have been shown to lower the levels of a number of inflammatory parameters, including high sensitivity C-reactive protein and matrix metalloproteinase (52,81–84).

In a recently published study comparing the efficacy of simvastatin, pioglitazone and the combination of both in patients with CVD, but without diabetes, the combination of pioglitazone and statin had additive and complimentary effects on a broad spectrum of inflammatory parameters and the lipoprotein profile independent of HbA1c level (52).

Conclusions

Type 2 diabetes manifests in an insulin-resistant individual when pancreatic β-cells are unable to produce sufficient insulin to overcome insulin resistance in the muscles and liver. Intervening early to attain glycaemic control and protect β-cell function is now regarded as central to improving long-term outcomes for patients with type 2 diabetes. The insulin secretagogue sulfonylureas and biguanides represented the mainstay of oral glucose-lowering therapy from their development in the 1940s to the 1990s. Today, these agents are still used and are proving especially useful in early combination therapy regimens with agents that improve glycaemic control by different molecular mechanisms. In patients treated with a sulfonylurea, there is a strong rationale to support the early combination with thiazolidinediones in type 2 diabetes. In addition to improving and maintaining glycaemic control, the thiazolidinediones reduce β-cell stress, improve insulin resistance and modify a variety of cardiovascular risk factors, including the abnormal lipid profile and increased low-grade inflammation activity associated with type 2 diabetes. The combined benefits of thiazolidinediones and sulfonylureas may delay the progression of type 2 diabetes and the need for exogenous insulin therapy, and may also offer benefits in terms of reduced risk of CVD.

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