Actos (pioglitazone): a new treatment for type 2 diabetes

JM Lawrence, JPD Reckless

Type 2 diabetes is increasingly common and can be difficult to control. By directly targeting insulin resistance, the thiazolidinediones offer a new mode of treatment. Here, the pharmacology, clinical trial evidence, side-effects and current clinical uses of pioglitazone are reviewed.

The prevalence of obesity, glucose intolerance and type 2 diabetes have increased and are continuing to rise in an increasingly sedentary westernized population worldwide. In the UK at least 2.5% of the population are now known to have type 2 diabetes, with higher rates in the elderly and some ethnic minority groups. It is characterized by the combination of β-cell failure and insulin resistance, with the contribution of each varying between individuals.

Patients are at risk of both microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (coronary, cerebrovascular and peripheral vascular) complications. Coronary heart disease (CHD) risk is at least twice that in the background population (Kannel and McGee, 1979), and is largely responsible for a one-third reduction in life expectancy from the time of diagnosis (Reckless, 1987). Much of the CHD risk is related to the clustering of established risk factors in these patients. 'Insulin resistance syndrome' describes the association of insulin resistance with impaired glucose tolerance or diabetes, hypertension, obesity (especially central), raised triglyceride levels, low high density lipoprotein (HDL)-cholesterol levels, raised uric acid levels and abnormalities in fibrinolysis (raised plasminogen activator inhibitor-1) and coagulation (raised fibrinogen) (Reaven, 1988).

CURRENT MANAGEMENT OF TYPE 2 DIABETES

The main aim of therapy in type 2 diabetes is to reduce the prevalence of complications. Recognizing and treating risk factors, particularly hypertension (Hansson et al, 1998; UK Prospective Diabetes Study Group, 1998a) and hypercholesterolaemia (Pyorala et al, 1997; Goldberg et al, 1998), has been shown to be effective in reducing macrovascular disease. Reducing high blood pressure also reduces microvascular disease, particularly retinopathy (UK Prospective Diabetes Study Group, 1998b). The UK Prospective Diabetes Study confirms the need not just to simply relieve symptoms of hyperglycaemia but to achieve 'tight control' of blood glucose (fasting plasma glucose <7 mmol/litre, haemoglobin A_{1c} (HbA_{1c}) <7%), for a 0.9% reduction in HbA_{1c} (7.9% to 7%) resulted in 25% less microvascular endpoints (UK Prospective Diabetes Study Group, 1998b). To achieve this modest improvement, treatment had to be stepped up during the study from a single agent to a combination of oral agents and ultimately to starting insulin in one third of patients over 10 years.

Sulphonylureas and metformin have been mainstays of oral treatment for years, alone or in combination. Sulphonylureas bind to β cells to stimulate insulin release (Groop, 1997). They are generally well tolerated, although weight gain may be a problem, and hypoglycaemia can occur, particularly if longer acting agents such as glibenclamide are used in elderly patients. The mechanism of action of metformin is less clear, reducing glucose absorption from the gut and hepatic glucose output while enhancing glucose uptake into peripheral tissues, particularly muscle and fat (Groop, 1997). Its use is not associated with weight gain or significant hypoglycaemia but approximately 15% of patients have to stop taking treatment as a result of diarrhoea.

THE THIAZOLIDINEDIONES

The thiazolidinediones (TZDs) are a new class of oral agent, with a novel mechanism of action, directly targeting insulin resistance. They bind to and stimulate the peroxisome proliferator-acti-

Dr JM Lawrence is Clinical Research Fellow, Diabetes and Lipid Research, Royal United Hospital, Bath BA1 3NG and **Dr JPD Reckless** is Honorary Reader in Biochemistry, University of Bath, and Consultant Diabetologist, Royal United Hospital, Bath

Correspondence to: Dr JPD Reckless

vated receptor gamma (PPARγ), one of a family of nuclear receptors modulating expression of genes involved in control of glucose and lipid metabolism. Levels of circulating triglycerides and non-esterified fatty acids fall, reducing insulin resistance through changes in the glucose–fatty acid (Randle) cycle. Changes in production and translocation of glucose transporters may also be important, as may a reduction in production of tumour necrosis factor α, which may play a part in the insulin resistance of type 2 diabetes (Day, 1999).

The first TZD on the market, troglitazone, was withdrawn because of liver toxicity (Day, 1999). Pioglitazone (Actos, Takeda, High Wycombe) and rosiglitazone (Avandia, GlaxoSmithKline, Uxbridge) have recently been licensed in the UK. Clinical trial evidence and experience, particularly in the USA, suggests that they are useful additions to current treatments, without evidence of hepatic toxicity to date. This review summarizes the pharmacology, clinical trial evidence, side-effects and current clinical usage of pioglitazone. The current licensed indications for its use in the UK and Europe are shown in *Figure 1*.

PHARMACOLOGY

Following oral administration pioglitazone is rapidly absorbed and this is unaffected by food. Peak plasma concentrations are seen within 2 hours, remain elevated for at least 24 hours after once-daily dosing and reach steady state concentrations within 7 days. Pioglitazone is extensively protein bound and largely eliminated by metabolism in the liver by the cytochrome P450 system, particularly isoenzymes 1A, 2C8/9 and 3A4. It is not an enzyme inducer and has low potential for drug interactions. Metabolism and drug clearance is unaltered in renal failure (Eckland and Danhof, 2000).

GLYCAEMIC EFFECTS

Clinical trials have been undertaken using pioglitazone both as monotherapy and in combination with sulphonylureas, metformin and insulin.

Figure 1. Current licensed indications for pioglitazone in the UK and Europe.

Monotherapy

Pioglitazone is effective as monotherapy in type 2 diabetes (*Figure 2*). In a trial of 408 patients randomized to placebo or pioglitazone 7.5 mg, 15 mg, 30 mg or 45 mg, all doses above 7.5 mg produced significant reductions in HbA_{1c} over the 26 weeks of the study (Aronoff et al, 2000). The effect of pioglitazone 45 mg was greater than that seen with lower doses and a greater reduction in HbA_{1c} was seen in the 127 patients who were drug naïve (no previous treatment with antidiabetic drugs) compared with those who had had previous antidiabetic drug treatment stopped 8 weeks before randomization. Patients were considered to have 'responded' to pioglitazone if HbA_{1c} fell by >0.6%. The overall response rate at 30 mg was 33% compared with 57% at 45 mg, with higher response rates of 52% and 68% on 30 mg and 45 mg in drug-naïve patients.

The dose–response effect was less marked in a second double-blind randomized forced titration study involving 260 patients for a total of 24 weeks (Buse, 2000). In the total study population, the HbA_{1c} fell by 1.48% relative to placebo (where HbA_{1c} rose by 0.9%) in those randomized to receive a maximum dose of 30 mg, compared with 1.53% in those randomized to receive 45 mg. Response rates in the two groups were also similar at 53% and 49%. As before, higher response rates were seen in drug-naïve patients, with 62.2% responding to 30 mg pioglitazone compared with 63.5% responding to the 45 mg dose. A higher response rate in drug-naïve patients (60.6% *vs* 48%) was also seen in a third trial over 16 weeks in 197 patients comparing 30 mg pioglitazone and placebo (Buse, 2000). The effect of pioglitazone monotherapy may be seen as early as 2 weeks after starting treatment and has been shown to persist in the longer term.

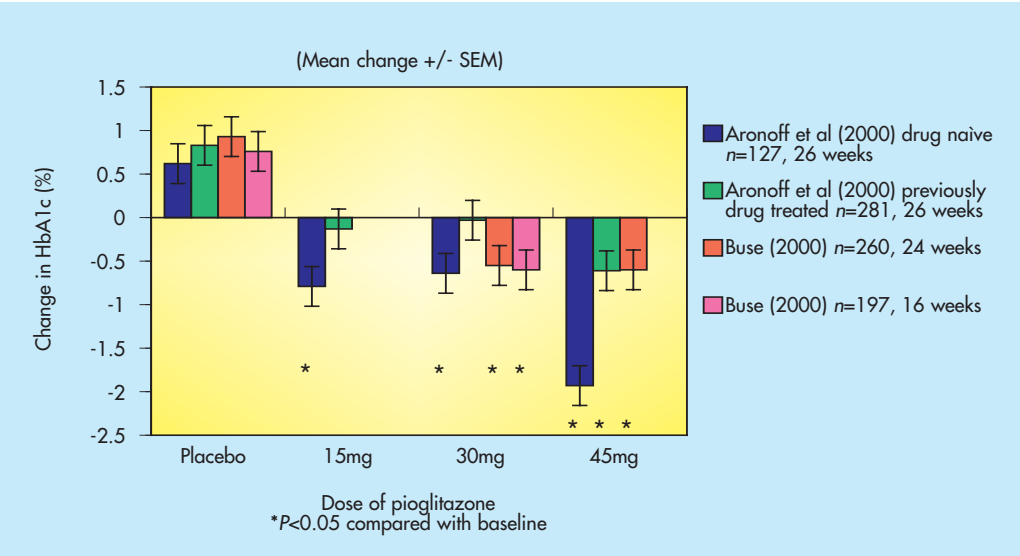
Combination therapy

Sulphonylurea: The effect of combination therapy (*Figure 3*) using a sulphonylurea and either 15 mg or 30 mg of pioglitazone has been compared in a randomized double-blind,

In the UK and Europe, pioglitazone is indicated only in oral combination treatment of type 2 diabetes in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy with either metformin or a sulphonylurea. It can be used:

- With metformin only in obese patients
- With a sulphonylurea only in patients for whom metformin in not tolerated or is contraindicated

In the UK and Europe pioglitazone is not licensed to be used alone or in combination with insulin. The maximum licensed dose is 30 mg.



placebo-controlled trial (Hanefeld and Göke, 2000). Five hundred and sixty patients with poorly controlled diabetes (HbA_{1c} >8%) on stable monotherapy with a sulphonylurea were randomized to receive additional pioglitazone or placebo. Seventy-two per cent of patients were receiving at least 50% of the maximum recommended dose of sulphonylurea at baseline. Over the 16 weeks of the trial the HbA_{1c} fell by 0.9% relative to placebo (where the HbA_{1c} increased by 0.1%) in those randomized to 15 mg of pioglitazone and by 1.3% in those randomized to 30 mg. Fifty-seven per cent of those randomized to pioglitazone 15 mg had a fall in HbA_{1c} of at least 0.6%, compared with 74.2% of those randomized to 30 mg.

Metformin

A similar trial where patients were randomized to receive either 30 mg of pioglitazone or placebo in combination with metformin demonstrated significant improvements in glycaemic control with combination therapy. HbA_{1c} fell by 0.83% relative to placebo (where HbA_{1c} rose by 0.19%) over 16 weeks (Einhorn et al, 2000).

Insulin

In combination with insulin, pioglitazone can significantly improve glycaemic control and may allow the insulin dose to be reduced. In a double blind, randomized, placebo-controlled trial, patients with type 2 diabetes suboptimally controlled (HbA_{1c} > 8%) on at least 30 units of insulin were randomized to additionally receive 0 mg, 15 mg or 30 mg of pioglitazone for 16 weeks (Buse, 2000). Combination of insulin

Figure 2. Effect of pioglitazone monotherapy on haemoglobin A_{1c} (HbA_{1c}). SEM = standard error of the mean.

with pioglitazone 15 mg resulted in a fall in HbA_{1c} of 0.73% compared with a 1% fall in those randomized to pioglitazone 30 mg while 16% of patients were able to reduce their insulin dose by >25%.

Effects of adding pioglitazone to metformin, a sulphonylurea or insulin persist in the long term but may not be seen until at least 4 weeks after initiating therapy, with the maximal effect being seen at 12 weeks.

There are currently no data available on the use of pioglitazone, metformin and a sulphonylurea in combination as triple therapy.

LIPID EFFECTS OF PIOGLITAZONE THERAPY

The dyslipidaemia of type 2 diabetes is typically characterized by the association of normal or slightly reduced total and low density lipoprotein (LDL) cholesterol with raised triglyceride and low HDL cholesterol levels (Reckless, 2001). This combination is responsible, at least in part, for the high rate of CHD seen in these patients. Pioglitazone has been shown to reduce triglycerides and raise HDL cholesterol while having largely no effect on LDL cholesterol (Buse, 2000) (*Figure 4*).

In monotherapy studies the reduction in triglycerides has varied markedly between 5 and 28% (Mathisen et al, 1999; Buse, 2000). In the largest monotherapy study involving 408 patients all doses of pioglitazone above 7.5 mg produced a similar reduction in triglycerides of approximately 9% (Aronoff et al, 2000). Associated with this was a rise in HDL choles-

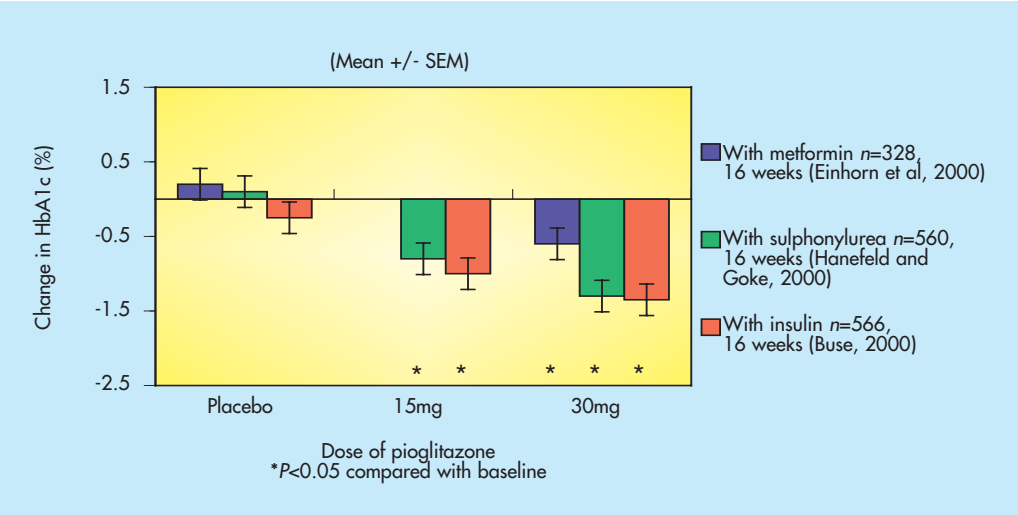


Figure 3. Effect of pioglitazone combination therapy on haemoglobin A_{1c} (HbA_{1c}). SEM = standard error of the mean.

terol of 14.1% in those treated with pioglitazone 15 mg (95% confidence interval (CI) 10–16.2%, $P<0.05$), of 12.2% in those treated with 30 mg pioglitazone (95% CI 8.1–16.3%, $P<0.05$) and of 19.1% in those treated with 45mg (95% CI 15–23.1%, $P<0.05$). Similar effects have been seen in combination studies with metformin (reduction in triglycerides 9.7%; 95% CI 2.5–16.9%, $P<0.05$, increase in HDL 10.2%; 95% CI 6.6–13.8%, $P<0.05$) (Einhorn et al, 2000) or with sulphonylureas (reduction in triglycerides 15.9%; 95% CI 9.4–22.4%, increase in HDL 12%; 95% CI 9.2–14.8% (Hanefeld and Göke, 2000). The net effect of the changes in lipids is a reduction in the cholesterol/HDL ratio, a predictor of CHD. It is also likely to reflect a change in LDL quality toward LDL1 and LDL2 away from the more atherogenic small, dense LDL3. Whether these lipid effects will translate into a reduction in CHD will only be known after long-term intervention studies.

OTHER POTENTIAL BENEFITS OF TZD THERAPY

TZDs might potentially reduce the risk of CHD through effects other than those on glucose and lipids (Parulkar et al, 2001). Troglitazone was shown to improve arterial endothelial function, reduce vascular smooth muscle proliferation and migration and to reduce plasminogen activator inhibitor I. These effects might be anticipated to result in reduced atherogenesis and indeed ultrasound studies have suggested a reduction in carotid intima thickness as little as 3 months after starting treatment with troglitazone. Fewer studies have been carried out with pioglitazone but evidence suggests it is likely to have similar effects. Whether these will impact on cardiovascular disease rates is unknown.

SIDE-EFFECTS

Pioglitazone is generally well tolerated with a low incidence of adverse events in clinical trials (Belcher and Matthews, 2000).

Hypoglycaemia

In view of its mechanism of action pioglitazone can cause hypoglycaemia and it is important to warn patients of this when starting treatment. This is more common in combination with a sulphonylurea or insulin than when pioglitazone is used as monotherapy or with metformin.

Weight gain

In all clinical trials, use of pioglitazone has been associated with weight gain. This tends to be more marked in combination with insulin (average weight gain 3.7 kg with 30 mg pioglitazone) and sulphonylureas (average weight gain 2.9 kg with 30 mg pioglitazone). The degree of weight gain does show some relationship to the dose of pioglitazone, but is more strongly associated with the inverse of the change in HbA_{1c}. It tends to occur early after instituting treatment and weight seems to stabilize in the longer term. It is interesting to note that the weight gain seen with pioglitazone is associated with a redistribution of fat from visceral to subcutaneous deposits. This may have important implications for cardiovascular risk, which is particularly associated with central adiposity, but this requires further study.

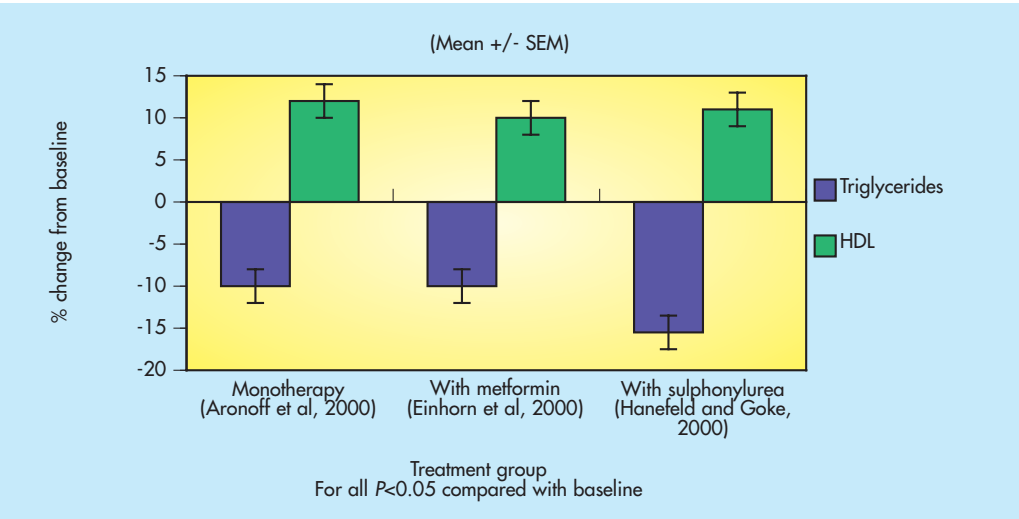


Figure 4. Effect on plasma lipids of pioglitazone 30 mg as monotherapy and combination therapy. HDL = high density lipoprotein; SEM = standard error of the mean.

Fluid retention and peripheral oedema

Pioglitazone can cause fluid retention and this is most commonly manifest as peripheral oedema. Oedema is usually mild and has not been associated with signs or symptoms of congestive cardiac failure in clinical trials, although patients with pre-existing heart failure were specifically excluded. Insulin therapy has been associated with peripheral oedema and it is not surprising that this side-effect is most common in patients treated with an insulin/pioglitazone combination.

Owing to fluid retention and haemodilution, use of pioglitazone may be associated with a small fall in haemoglobin and haematocrit. Across all clinical trials the average fall in haemoglobin was approximately 0.4 g/dl relative to placebo.

Cardiac effects

While all TZDs have been associated with concentric cardiac hypertrophy in toxicology studies in animals, echocardiographic follow-up in clinical trials has shown no evidence of this in man. In all trials there has been no difference in cardiovascular adverse events between those randomized to placebo and pioglitazone.

Liver toxicity

Concerns regarding possible liver toxicity with TZDs were raised before the withdrawal of troglitazone. To date pioglitazone has been used by more than 1 million people in the United States and there have been no reports of serious liver toxicity. In clinical trials the prevalence of abnormal alanine transaminase (ALT) levels (> 3 times the upper limit of normal; ULN) was no higher in those randomized to pioglitazone compared with placebo. Nevertheless, monitoring of liver function tests is advised. Pioglitazone should not be started if baseline ALT is > 2.5 times ULN. Liver function tests should be checked 2-monthly in the first year of treatment and periodically thereafter. Pioglitazone should be stopped if ALT increases to > 3 times ULN.

CLINICAL USE

In the UK and Europe pioglitazone is currently licensed in oral combination therapy in patients with insufficient glycaemic control despite maximum tolerated doses of monotherapy with either metformin or a sulphonylurea. It can be used in combination with metformin only in obese subjects and with a sulphonylurea only where metformin is not tolerated or contraindicated (*Figure 1*). In contrast, in the United States pioglitazone is licensed for use as monotherapy, and in combination with metformin, sulphonylureas and insulin.

Pioglitazone is taken once a day either with or without food, and doses of either 15 or 30 mg are currently licensed in the UK. When initiating therapy the doses of metformin and sulphonylurea can be kept the same, although doses may need to be reduced if hypoglycaemia occurs, particularly with sulphonylureas. It is important to tell patients that effects may not be seen for several weeks after starting therapy and it is also important to remember that not all patients will respond. If no change in glucose values has occurred by 12 weeks on 30 mg pioglitazone then alternative treatments should be considered. No change in dosage is necessary in the elderly or in patients with impaired renal function down to a creatinine clearance of 4 ml/min.

Pioglitazone should not be used in pregnancy or during breast-feeding and is not recommended in patients under 18 years old as no data exist in this group.

Owing to fears regarding fluid retention, and possibly precipitating heart failure, pioglitazone is currently contraindicated in combination with insulin in the UK and Europe, although about 20% of treated patients in the USA are on this combination. It is also contraindicated in patients with any degree of heart failure (New York Heart Association stages I to IV) and where hepatic impairment is present (see liver toxicity).

Pioglitazone received approval for use from the National Institute of Clinical Excellence in the UK in March 2001 (National Institute of Clinical Excellence, 2001) .

CONCLUSIONS

Pioglitazone is a TZD, a new class of oral hypoglycaemics used in type 2 diabetes which directly target insulin resistance. Evidence suggests that it is effective alone or in combination with metformin, sulphonylurea or insulin. Although licensed for all these indications in the USA, the current licence in Europe and the UK is more restrictive. It is generally well tolerated although it is important to be aware of the risk of hypoglycaemia, the likelihood of weight gain and the risk of peripheral oedema. It can be used in a broad group of patients including the elderly and those with renal failure (minimum creatinine clearance 4 ml/min). In addition to its effects on plasma glucose, it appears to have favourable effects on plasma lipids, reducing triglycerides and raising HDL cholesterol. To date there has been no evidence of serious liver toxicity although monitoring of liver function tests is advised. **HM**

KEY POINTS

- By directly targeting insulin resistance, pioglitazone offers a useful addition to currently available treatments for type 2 diabetes.
- Pioglitazone is currently licensed in the UK for use in combination with metformin or a sulphonylurea.
- Pioglitazone produces potentially beneficial effects on the dyslipidaemia associated with type 2 diabetes.
- No significant drug interactions have been reported and pioglitazone can be used in renal impairment.
- Side effects are uncommon but patients should be made aware of the risk of hypoglycaemia, weight gain and peripheral oedema when starting therapy.
- Pioglitazone is contraindicated in heart failure and in patients with pre-existing liver disease.
- Although liver toxicity has not been reported, as with all thiazolidinediones monitoring of liver function tests is mandatory.
- Pioglitazone has now been reviewed and received approval from the National Institute of Clinical Excellence.

Conflict of interest: Departmental research has been sponsored by Takeda Pharmaceuticals and GlaxoSmithKline. JPDR has received consultancy fees from Takeda Pharmaceuticals.

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