Drugs 2000 Aug; 60 (2): 333-343
0012-6667/00/0008-0333/$25.00/0

Pioglitazone

Peter S. Gillies and *Christopher J. Dunn*

Adis International Limited, Auckland, New Zealand

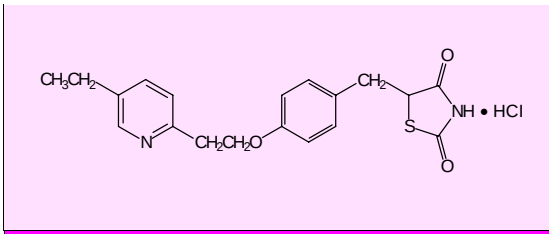
Contents

Abstract

- Pioglitazone is an orally administered insulin sensitising thiazolidinedione agent that has been developed for the treatment of type 2 diabetes mellitus.
- Pioglitazone activates the nuclear peroxisome proliferator activated receptor-γ (PPAR-γ), which leads to the increased transcription of various proteins regulating glucose and lipid metabolism. These proteins amplify the post-receptor actions of insulin in the liver and peripheral tissues, which leads to improved glycaemic control with no increase in the endogenous secretion of insulin.
- In placebo-controlled clinical trials, monotherapy with pioglitazone 15 to 45 mg/day has been shown to decrease blood glycosylated haemoglobin (HbA_{1c}) levels in patients with type 2 diabetes mellitus.
- The addition of pioglitazone 30 mg/day to pre-existing therapy with metformin, or of pioglitazone 15 or 30 mg/day to sulphonylurea, insulin or voglibose therapy, has been shown to decrease HbA_{1c} and fasting blood glucose levels significantly in patients with poorly controlled type 2 diabetes mellitus.
- Pioglitazone has also been associated with improvements in serum lipid profiles in randomised placebo-controlled clinical studies.
- The drug has been well tolerated by adult patients of all ages in clinical studies. Oedema has been reported with monotherapy, and pooled data have shown hypoglycaemia in 2 to 15% of patients after the addition of pioglitazone to sulphonylurea or insulin treatment. There have been no reports of hepatotoxicity.

Features and properties of pioglitazone (AD 4833, U 72107, U 72107A, U72107E)

Indications		
Type 2 (non–insulin-dependent) diabetes mellitus		
Mechanism of action		
Antihyperglycaemic	Activates nuclear peroxisome proliferative activated receptor-γ (PPAR-γ)	
Dosage and administration		
Usual dosage in clinical trials	15 to 45 mg/day	
Route of administration	Oral	
Frequency of administration	Once daily	
Pharmacokinetic profile (steady state in young healthy adults)		
	15 mg/day	30 mg/day
Peak plasma concentration (mg/L)	0.7	1.7
Time to peak plasma concentration (hours)	2.5	3
Area under the plasma concentration-time curve to 24 hours after administration (mg/L • h)	4.8	15.3
Elimination half-life (hours)	3.3	4.9
Metabolism	Hepatic (predominantly via cytochrome P450 enzymes)	
Adverse events		
Most frequent or clinically relevant	Oedema, upper respiratory tract infection, headache sinusitis. Hypoglycaemia only in combination with insulin or sulphonylurea	



Pioglitazone

Pioglitazone is a member of the thiazolidinedione group of drugs developed for the treatment of type 2 (non–insulin-dependent) diabetes mellitus, a disorder associated with a number of metabolic abnormalities that include impaired insulin secretion and insulin resistance. Insulin resistance leads to decreased glucose utilisation by the peripheral tissues and increased hepatic glucose output, and is an important underlying metabolic abnormality in many patients with type 2 diabetes mellitus. It is believed to be a key component of the metabolic syndrome ('syndrome X'), which is characterised by dyslipidaemia, hypertension, atherosclerosis, central obesity and impaired glucose metabolism (reviewed by Saltiel and Olefsky[1] and Granberry and Fonseca[2]). The thiazolidinediones act by sensitising the liver and peripheral tissues to the effects of insulin, which results in improved insulin-mediated glucose disposal.

Pioglitazone was administered orally in all animal and human studies discussed in this profile.

1. Pharmacodynamic Profile

The thiazolidinediones have been shown to bind with high affinity to and activate the nuclear peroxisome proliferator activated receptor-γ (PPAR-γ).[3] The PPARs are members of the steroid receptor family and are thought to be involved in the modulation of the expression of a number of genes coding for proteins involved in glucose and lipid metabolism (reviewed by Saltiel and Olefsky[1]). PPAR-γ activation also stimulates differentiation of preadipocytes[4] and bone marrow stromal cells[5] into mature adipocytes. Most of the changes induced by the thiazolidinediones appear to be orchestrated via the activation of this receptor.[3,6,7] Studies show that pioglitazone stimulates the uptake of glucose and fatty acids into cells by promoting the synthesis and expression of cellular glucose and fatty acid transporters.

Mechanism of Action

- Pioglitazone has been shown to increase insulin receptor expression in adipocytes[8,9] and hepatocytes.[10] However, the drug does not appear to affect insulin binding to or expression of insulin receptors in skeletal muscle.[11] Pioglitazone therefore appears to act largely via enhancement of the intracellular signalling cascade induced by insulin after binding of the hormone to its receptor.[11,12]

- Expression of the glucose transporter proteins GLUT1 and GLUT4 was increased 10- and 7-fold, respectively, relative to baseline in 3T3-F442A preadipocyte cultures treated with pioglitazone 1 μmol/L and insulin 1 mg/L.[13] GLUT4 expression was increased in epididymal fat cells in KKA^y mice (an animal model of insulin-resistant type 2 diabetes mellitus) after treatment with pioglitazone 20 mg/kg/day for 4 days ($p < 0.01$ *vs* untreated KKA^y mice).[14]

- Expression of fatty acid translocase and fatty acid transport protein in white adipose tissue was increased relative to untreated controls in KKA^y mice who were fed a diet containing pioglitazone 0.03% for 8 days.[15] Greater enhancement of expression of these proteins was reported with pioglitazone than with troglitazone or the PPAR-α activator clofibrate.[15]

- Pioglitazone 20 mg/kg/day induced adipogenesis and alterations in adipocyte morphology that resulted in the development of smaller and more insulin-sensitive cells in obese (*fa/fa*) Zucker rats.[16] Enhanced expression of glucose transporters and stabilisation of transporter messenger RNA transcripts accompanied near-complete differentiation of 3T3-F442A preadipocytes into lipid-accumulating adipocytes in cultures treated with pioglitazone 1 mmol/L in the presence of insulin 1 mg/L.[13]

• Pioglitazone augments the hepatic response to insulin, as shown by enzyme effects in animal models. Four days' treatment with pioglitazone 20 mg/kg/day altered hepatic activities of glucose-6-phosphate dehydrogenase, glucose-6-phosphatase and phosphoenol pyruvate carboxykinase in KKA^y mice to levels similar to those in nondiabetic C57 mice, and amplified insulin-enhanced expression of glucokinase (by a factor of 2.91 *vs* controls) in rats with streptozotocin-induced diabetes mellitus.[17]

• Insulin-stimulated glycogen synthesis and glycolysis in isolated soleus muscles and glucose oxidation and lipogenesis in adipocytes were increased ($p < 0.05$ *vs* controls) after treatment of Wistar fatty rats with pioglitazone 0.3 to 3 mg/kg/day for 7 days.[18]

• After incubation for 18 hours with insulin 0.1 μmol/L and pioglitazone 5 μmol/L, protein phosphatase-1 (the enzyme that activates glycogen synthase) activity was increased significantly ($p < 0.01$ *vs* controls) in hepatocytes from rats with streptozotocin-induced diabetes mellitus.[19]

• Pioglitazone 3 mg/kg/day decreased plasma and skeletal muscle levels of tumour necrosis factor-α (TNFα) in a time-dependent manner in Wistar fatty rats.[20] Both TNFα levels and neutral sphingomyelinase (SMase) activity were reduced after 4 days' treatment to levels seen in lean rats. The results suggest that increased release of TNFα and subsequent activation of SMase in skeletal muscle are associated with metabolic abnormalities in diabetes mellitus and obesity, and that the suppression of TNFα production accounts in part for the antidiabetic activity of pioglitazone.[20]

Effects on Glucose and Lipid Metabolism

Animal Studies

• Pioglitazone has been shown to decrease plasma glucose, insulin and/or triglyceride levels in various diabetic and insulin-resistant animal models including Wistar fatty rats,[21] *fa/fa* Zucker rats,[22] KKA^y diabetic mice[23] and insulin-resistant rhesus monkeys.[24]

• Relative to untreated controls, pioglitazone 20 mg/kg/day administered for 4 days reduced plasma glucose and insulin levels by 44 and 60%, respectively, in KKA^y diabetic mice ($p < 0.05$).[23]

• After 10 days' treatment, pioglitazone 3 mg/kg/day reduced fasting plasma glucose, serum insulin and serum triglyceride levels by 19, 64 and 44%, respectively, in obese, insulin-resistant rhesus monkeys (all $p < 0.05$ *vs* pretreatment placebo phase).[24] These changes were accompanied by statistically significant falls in systolic and mean arterial pressures.

• Markedly improved insulin action and glucose utilisation were accompanied by weight gain after 28 days' treatment with pioglitazone 10 mg/kg/day in *fa/fa* Zucker rats.[7] Glucose utilisation (measured by the 2-deoxyglucose technique) was increased 3- to 4-fold in adipose tissue depots ($p < 0.01$ *vs* untreated controls) and 1.7-fold in soleus muscle ($p < 0.05$ *vs* controls). The mean bodyweight gain in treated rats was 1.7 times that in untreated controls over the study period ($p < 0.05$).[7]

• Pioglitazone 20 mg/kg/day for 1 month significantly decreased fasting plasma glucose and insulin levels in *fa/fa* Zucker rats but not in lean rats, and increased net energy intake in both types of rat (all $p < 0.05$ *vs* controls).[22] Basal metabolic rates were unchanged. Relative to controls, weekly growth rates increased with pioglitazone treatment (by 32 and 67% in lean and obese rats, respectively). Analysis of fat and lean body masses indicated that protein accumulation was preferentially stimulated by pioglitazone in lean, insulin-responsive rats, whereas lipid accumulation predominated in obese animals.[22]

• Administration of pioglitazone 1 mg/kg/day for 14 days decreased plasma glucose and triglyceride levels (to 57 and 59%, respectively, of levels in untreated control animals), but did not affect plasma insulin levels or skeletal muscle glycogen content in male Wistar fatty rats.[25] Pioglitazone monotherapy was also associated with increased food intake and gains in bodyweight. Addition of metformin 300 mg/kg/day reduced plasma insulin

levels (to 70% of control levels) and suppressed food intake increases and bodyweight gains.[25]

Studies in Humans

- Pioglitazone 30 mg/day for a mean 87 days was associated with significant increases in insulin-stimulated glucose disposal (from 5.5 to 8.3 mg/kg/min; $p < 0.01$ *vs* baseline) under euglycaemic, hyperinsulinaemic clamp conditions in 20 patients with type 2 diabetes mellitus.[26] Recruited patients were not obese, with a mean body mass index (BMI) of 23.9 kg/m^2; diabetes was controlled by diet alone in 3 patients and by diet plus sulphonylurea treatment in 17.

- Pioglitazone significantly ($p < 0.01$ *vs* baseline) reduced fasting plasma glucose (from 11.0 to 8.9 mmol/L), fasting serum insulin (from 83 to 66 pmol/L), serum free fatty acid (from 1.3 to 0.8 mEq/L) and serum triglyceride levels (from 1.9 to 1.3 mmol/L). Serum levels of high density lipoprotein (HDL)-cholesterol increased from 1.2 to 1.5 mmol/L ($p < 0.01$), but BMI did not change significantly after pioglitazone treatment.[26]

- Pioglitazone 30 mg/day enhanced splanchnic glucose uptake under euglycaemic hyperinsulinaemic clamp conditions in patients with type 2 diabetes mellitus controlled by diet alone or diet and sulphonylurea treatment in a randomised, placebo-controlled double-blind trial.[27] After 12 weeks' treatment in 21 patients, the mean glucose infusion rate before an oral glucose load increased from 8.2 to 9.2 mg/kg/min ($p = 0.003$ *vs* baseline), and splanchnic glucose uptake (expressed as a proportion of oral glucose load) increased from 28.5 to 59.4% ($p = 0.01$ *vs* baseline and $p = 0.042$ *vs* placebo). Placebo treatment in 9 patients produced no significant changes in either of these parameters.

Cardiovascular Effects

- Pioglitazone 20 mg/kg/day for 7 weeks prevented the development of hypertension and reduced plasma insulin levels (by 70 and 37%, respectively, relative to untreated controls) in rats fed diets with high fat or glucose content.[28] The same dosage of pioglitazone for 4 weeks significantly ($p < 0.01$ *vs* untreated controls) reduced fasting and postprandial plasma insulin levels and systolic and mean blood pressures in spontaneously hypertensive rats.[29]

- Pioglitazone has been shown to possess direct, insulin-independent vasorelaxant properties. Addition of the drug at a rate of 0.1 mg/g to feed given to spontaneously hypertensive rats for 6 weeks decreased mean systolic blood pressure (by 23%; $p < 0.001$ *vs* untreated controls) and significantly ($p < 0.05$ *vs* controls) attenuated contractile responses of mesenteric arterial and aortic tissue to arginine vasopressin and noradrenaline (norepinephrine).[30]

- At a daily dosage of approximately 22 mg/kg, pioglitazone prevented increases in blood pressure seen in rats given a normal or high-fructose diet.[31] *In vitro* data showed attenuation by pioglitazone 20 mg/L of the contractile effects of noradrenaline 25 to 150 nmol/L, potassium chloride 28 mmol/L or arginine vasopressin 0.66 nmol/L in rat aortic rings.[31]

- In a vehicle-controlled study, pioglitazone 3 mg/kg/day for 13 weeks significantly lowered systolic blood pressure, decreased proteinuria, improved histological renal injury scores with respect to glomerulosclerosis and renal arteriosclerosis, and attenuated aortic medial wall thickening in geneticallly obese Wistar fatty rats with insulin resistance.[32]

- *In vitro*, pioglitazone at concentrations of 0.01 and 1 mg/L inhibited the proliferation induced by basic fibroblast growth factor of mouse aortic endothelial cells, but not that induced by insulin.[33] In addition, pioglitazone 10 mg/kg/day inhibited balloon catheterisation-induced intimal thickening in carotid arteries of male Wistar fatty and lean rats.[34] This effect was enhanced in the presence of diabetes.

- Pioglitazone 3 mg/kg/day also reduced injury-induced neointimal thickening in common carotid arteries of Wistar rats and attenuated uptake of bromodeoxyuridine (a marker of DNA synthesis in neointima) in mesenteric arterial tissue from spontaneously hypertensive rats.[35] Overall, these re-

sults show vasculoprotective effects of pioglitazone in both diabetic and nondiabetic animal models that are thought to be related to inhibition of proliferation of vascular smooth muscle cells.

• Pioglitazone (300 parts per million added to 200 g/day of feed) markedly decreased lipid deposition in the aortas of rabbits fed with diets containing 0.5% cholesterol for 10 weeks (lipid deposition area 15% with pioglitazone *vs* 57% in controls).[36] The drug had no significant effect on serum levels of total and HDL-cholesterol or triglyceride, but was associated with tendencies towards decreased blood pressure and lipid peroxide levels. These results indicate overall inhibition of atherosclerosis by pioglitazone.

Other Effects

• In addition to reducing hyperglycaemia, hyperlipidaemia and hyperinsulinaemia, pioglitazone 3mg/kg/day attenuated the development of microalbuminuria and the histological changes associated with diabetic nephropathy when administered to Wistar fatty rats from 7 to 15 weeks of age.[37]

• When given in feed for 48 hours after growth hormone treatment (200 μg/day subcutaneously for 3 days), pioglitazone 20 mg/kg/day ameliorated the hyperglycaemic, hyperinsulinaemic effects of the hormone without interfering with its growth-stimulating activity in female genetically obese (*ob/ob*) mice.[38]

2. Pharmacokinetic Profile

• At steady state, maximum plasma drug concentrations (C_{max}) were 0.7 and 1.2 mg/L, and times to C_{max} (t_{max}) were 4.8 and 3.7 hours, for pioglitazone 15 and 30 mg/day, respectively, in 11 healthy elderly male volunteers (mean age 70.4 years) who were randomised to receive either dosage of pioglitazone for 7 days.[39] Respective C_{max} values for total active compound (unchanged pioglitazone plus active metabolites MII, MIII and MIV) were 1.4 and 2.5 mg/L.[39]

• After 7 days' treatment, elimination half-lives ($t_{½\beta}$) were 4.9 and 4 hours and areas under plasma drug concentration versus time curves over 24 hours after administration (AUC_{24}) were 6 and 10.2 mg/L · h for pioglitazone 15 and 30 mg/day, respectively (parent compound only). Corresponding AUC_{24} values for total active compound (parent drug plus active metabolites) were 23.3 and 39.7 mg/L · h.[39]

• In 12 healthy young adults (mean age 23 years) who received pioglitazone 15 or 30 mg/day for 8 days, steady-state C_{max} values were 0.7 and 1.7 mg/L and t_{max} 2.5 and 3 hours with pioglitazone 15 and 30 mg/day, respectively.[39]

• Steady-state $t_{½\beta}$ values in young volunteers for parent drug only were 3.3 and 4.9 hours, and AUC_{24} values were 4.8 and 15.3 mg/L · h, for pioglitazone 15 and 30 mg/day, respectively.[39] $t_{½\beta}$ for total pioglitazone is reported to be 16 to 24 hours.[40]

• Ninety-six hours after the final dose in elderly volunteers, 28.7% of the total dose in the 15 mg/day recipients and 23.3% in the 30 mg/day recipients had been excreted in the urine as conjugated (MI + MIV) or unconjugated (MV) metabolites.[39]

• Pioglitazone undergoes extensive hepatic metabolism, predominantly via by the cytochrome P450 (CYP) 2C8 system. Secondary pathways include CYP3A4, CYP2C9 and CYP1A1/2.[41,42]

• A study in 21 individuals with severe [creatinine clearance (CL_{CR}) <1.8 L/h] or moderate (CL_{CR} 1.8 to 3.6 L/h) renal impairment and 6 healthy volunteers showed AUC values for pioglitazone (single and multiple daily doses of 45mg) and its major metabolites MIII and MIV to decrease with increasing impairment of renal function.[43] This suggests increased hepatic clearance of pioglitazone secondary to reduced protein binding in plasma, with no net change in free plasma drug concentrations, in patients with renal impairment who receive the drug.[43]

Drug Interactions

• Administration of pioglitazone 30 mg/day for 7 days had no significant effect (relative to baseline) on the pharmacokinetic characteristics of glibenclamide 5 to 10 mg/day or gliclazide 160 mg/day in a study in 9 patients with type 2 diabetes mellitus.[44] The extent of protein binding of the 2 sulphonylureas was not affected by the presence of pioglitazone.[44]

• Similarly, administration of pioglitazone 45 mg/day (single and multiple doses) had no significant effect on the pharmacokinetic or pharmacodynamic characteristics of warfarin, phenprocoumon, glipizide, metformin or digoxin in healthy volunteers.[41] The lack of effect of pioglitazone on the pharmacokinetics and action of warfarin and on urinary 6β-hydroxycortisol/cortisol ratios suggested no induction or inhibition of CYP enzymes 3A4, 1A1/2 or 2C9.[41]

• Lack of induction or inhibition of hepatic enzyme systems was also indicated by data showing no statistically or clinically significant effect of pioglitazone 45 mg/day on the pharmacokinetics of combinations of ethinylestradiol/norethindrone or ethinylestradiol/estrone as used in oral contraceptive or hormone replacement therapy regimens.[45]

3. Clinical Trials

Pioglitazone has been evaluated in the treatment of type 2 diabetes mellitus in multicentre, randomised, double-blind, placebo-controlled trials in which pioglitazone was given as monotherapy[46-48] or in combination with another antidiabetic agent.[49-51] In all trials, pioglitazone was administered orally once daily.

Most of the studies reported formed part of a series carried out in the US; in those in which pioglitazone was combined with a second antidiabetic drug,[49-51] any additional antidiabetic agents were withdrawn and patients were required to have been on a stable dosage of the second drug for at least 6 weeks before starting pioglitazone. All patients recruited in these combination therapy studies had baseline glycosylated haemoglobin (HbA_{1c}) levels of at least 8%.

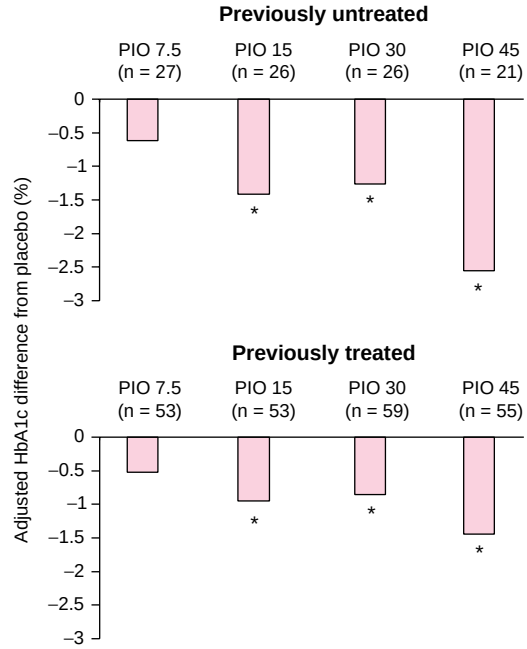


Fig. 1. Effect of pioglitazone (PIO) on mean glycosylated haemoglobin (HbA_{1c}) levels in blood. Of 399 evaluable patients with type 2 diabetes mellitus in this double-blind placebo-controlled study, 274 had received previous treatment (defined as antidiabetic drug therapy that was stopped 8 weeks before randomisation). PIO 7.5, 15, 30 or 45mg or placebo was given once daily for 26 weeks. Mean baseline HbA_{1c} levels ranged from 9.04 to 9.96% in the previously untreated patients and from 10.3 to 10.87% in the previously treated patients. Results are shown as adjusted differences from placebo at week 26.[47] * $p \leq 0.05$ *vs* placebo.

Pioglitazone Monotherapy

• Clinical efficacy of pioglitazone in terms of reduction of HbA_{1c} levels was shown in a double-blind dose-ranging US study in which 399 evaluable patients (of whom 274 had received previous antidiabetic medication that was stopped 8 weeks before randomisation) were randomised to receive pioglitazone 7.5, 15, 30 or 45 mg/day or placebo for 26 weeks.[47] Mean HbA_{1c} levels decreased significantly ($p \leq 0.05$ *vs* placebo) with pioglitazone

15, 30 or 45 mg/day in both previously untreated and previously treated patients (fig. 1).[47]

• Pioglitazone 30 mg/day for 16 weeks significantly decreased mean HbA_{1c} (adjusted change *vs* placebo = –1.37%; $p \leq 0.05$), fasting blood glucose (FBG) and triglyceride levels in a randomised double-blind study in 197 US patients with type 2 diabetes mellitus.[46] In terms of HbA_{1c}, 48% of pioglitazone and 11% of placebo recipients responded to treatment (defined as reduction *vs* HbA_{1c} baseline of ≥0.6%). Corresponding response rates in terms of FBG levels were 61 and 23%, respectively (defined as reduction *vs* baseline of ≥1.7 mmol/L).

• Pioglitazone treatment significantly increased mean fasting HDL-cholesterol levels, but did not significantly affect total cholesterol and low density lipoprotein (LDL)-cholesterol levels in blood.[46] Significant adjusted changes relative to placebo with pioglitazone are summarised in figure 2.

• In a randomised double-blind Japanese study, 134 evaluable patients received pioglitazone 30 mg/day (n = 68) or placebo (n = 66), together with pre-existing diet and exercise therapy, for 12 weeks.[48] Overall mean pretreatment levels of HbA_{1c} and FBG were 9.3% and 10.2 mmol/L, respectively. After 12 weeks' therapy, the mean HbA_{1c} level decreased by 1.08% and FBG by 1.6 mmol/L relative to baseline in patients who received pioglitazone. In the placebo group, HbA_{1c} was unchanged and FBG increased by 0.3 mmol/L. Differences between groups were significant for changes in both parameters ($p \leq 0.01$).

• Differences between active treatment and placebo in changes over 12 weeks in fasting triglyceride, total cholesterol and free fatty acid levels in blood were not statistically significant in the above study.[48] However, a significantly greater increase in the mean HDL-cholesterol level was reported in patients who received pioglitazone than in placebo recipients (8.6 *vs* 1.6 mmol/L; $p \leq 0.01$).

• Although the thiazolidinediones have not yet been compared in controlled clinical studies, a preliminary comparison of pioglitazone 45mg (n = 30), rosiglitazone 8mg (n = 36) and troglitazone 600mg (n = 35) daily in 3 consecutive series of patients has shown similar reductions in HbA_{1c} levels with all 3 drugs after 2 to 4 months' treatment.[52]

• Of the 3 drugs, pioglitazone had the most beneficial effect on blood lipid profiles over 2 to 4 months.[52] The mean HDL-cholesterol level was increased by 12.8% with pioglitazone; respective 3.2 and 1.1% increases were reported with troglitazone and rosiglitazone. A 1.1% decrease in the mean LDL-cholesterol level with pioglitazone contrasted with 6.6 and 11.2% increases with troglitazone and rosiglitazone, respectively. There was also a 10.1% decrease in the mean triglyceride level in patients receiving pioglitazone; this was contrasted with a 2.2% decrease with troglitazone and a 27% increase with rosiglitazone.

Combination with Metformin

• Combination treatment with pioglitazone 30 mg/day and metformin (≥2 g/day in 40% of patients) for 16 weeks significantly ($p \leq 0.05$) decreased HbA_{1c} and FBG levels in a double-blind

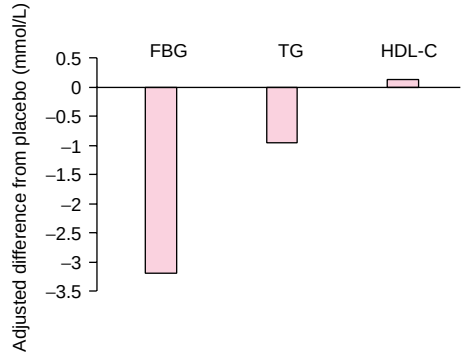


Fig. 2. Effects of pioglitazone (PIO) monotherapy on fasting blood glucose (FBG), triglyceride (TG) and high density lipoprotein-cholesterol (HDL-C) levels. 197 patients with type 2 diabetes mellitus received PIO 30 mg/day or placebo for 16 weeks in a randomised double-blind clinical study.[46] Adjusted changes at 16 weeks relative to placebo are shown for mean parameters; all were statistically significant ($p \leq 0.05$).

study in 328 patients.[49] Adjusted reductions versus metformin plus placebo were 0.83% and 2.1 mmol/L, respectively.

• Mean fasting triglyceride levels in blood were significantly reduced and mean HDL-cholesterol levels significantly increased with the addition of pioglitazone to metformin therapy in the above study ($p \leq 0.05$ *vs* metformin plus placebo) [fig. 3].[53] Concomitant treatment with pioglitazone had no statistically significant effect on fasting total cholesterol and LDL-cholesterol levels.

Combination with a Sulphonylurea

• The addition of pioglitazone 15 or 30 mg/day to sulphonylurea therapy significantly ($p \leq 0.05$) decreased HbA_{1c} (by 0.9 and 1.3%, respectively) and FBG (by 2.2 and 3.2 mmol/L, respectively) levels relative to sulphonylurea plus placebo after 16 weeks in a double-blind study in 560 patients with poorly controlled type 2 diabetes mellitus.[50]

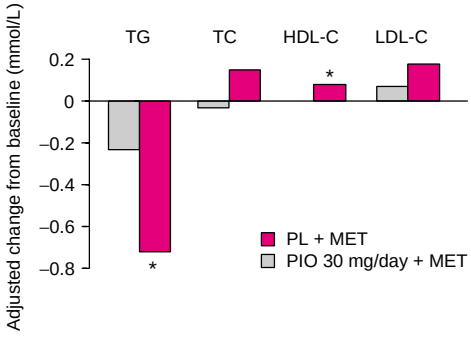


Fig. 3. Effects of addition of pioglitazone (PIO) to pre-existing metformin (MET) therapy on fasting blood lipid profiles in patients with type 2 diabetes mellitus. 328 patients were randomised in a double-blind fashion to PIO 30 mg/day (n = 168) or placebo (PL) [n = 160] in addition to MET for 16 weeks.[53] Adjusted changes from baseline with PIO + MET and PL + MET at 16 weeks are shown for mean parameters. **HDL-C** = high density lipoprotein-cholesterol level; **LDL-C** = low density lipoprotein-cholesterol level; **TC** = total cholesterol level; **TG** = triglyceride level. ***** $p \leq 0.05$ vs PL + MET.

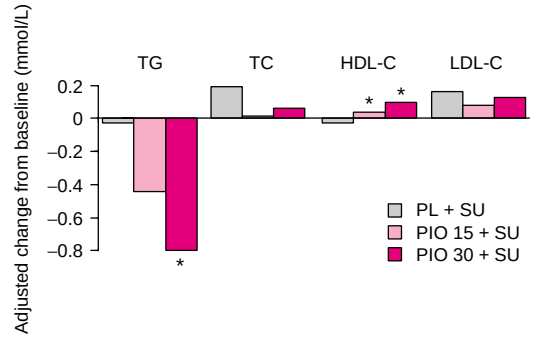


Fig. 4. Effects of addition of pioglitazone (PIO) to pre-existing sulphonylurea (SU) therapy on clinical parameters in patients with type 2 diabetes mellitus. 560 patients were randomised in a double-blind fashion to PIO 15 (n = 184) or 30 mg/day (n = 189) or placebo (PL) [n = 187] in addition to SU for 16 weeks.[50,54] Percentage changes at 16 weeks relative to baseline are shown for mean parameters. **HDL-C** = serum high density lipoprotein-cholesterol level; **LDL-C** = serum low density lipoprotein-cholesterol level; **TC** = serum total cholesterol level; **TG** = serum triglyceride level. * $p \leq 0.05$ *vs* PL + SU.

• In the above study, there was a significant decrease ($p \leq 0.05$) in mean fasting blood triglyceride levels with the addition of pioglitazone 30 mg/day to sulphonylurea therapy (fig. 4).[54] Significant increases in fasting HDL-cholesterol levels were noted with both dosages of pioglitazone. The addition of pioglitazone induced no significant changes relative to placebo in mean total cholesterol or LDL-cholesterol levels (fig. 4). Dosages and names of sulphonylureas used were not reported, but 72% of patients were receiving ≥50% of the maximum recommended daily dosage.[50,54]

Combination with Insulin

• Sixteen weeks' therapy with pioglitazone 15 or 30 mg/day in combination with insulin significantly ($p \leq 0.05$) decreased mean HbA_{1c} (by 0.73 and 1%, respectively) and FBG (by 1.9 and 2.7 mmol/L) levels compared with insulin combined with placebo in a double-blind study in 566 patients with type 2 diabetes mellitus.[51] At randomisation, all patients were receiving ≥30 units of insulin per day, with 50% receiving ≥60.5 units/day.

Of the patients randomised to pioglitazone 30 mg/day, 16% experienced a decrease in insulin requirements of more than 25%.

Combination with Voglibose

• Pioglitazone was added to pre-existing treatment with the α-glucosidase inhibitor voglibose (with or without sulphonylurea) in 42 evaluable Japanese patients with poorly controlled type 2 diabetes mellitus in a noncomparative study.[55] All patients had a baseline FBG level of at least 8.3 mmol/L, 16 were receiving voglibose alone, and 36 were receiving voglibose plus a sulphonylurea. All patients except one received pioglitazone 30mg once daily before breakfast in this 12-week study. One patient who was on voglibose only before the trial received pioglitazone 15mg once daily.

• At week 12, the mean FBG level had decreased by 19.2% from baseline. The mean HbA_{1c} level decreased in a linear fashion from 9.7 to 8.2% at week 12. Both results were statistically significant. Relative to baseline, serum free fatty acid and triglyceride levels decreased and HDL-cholesterol levels increased to a statistically significant extent after 12 weeks' pioglitazone therapy.[55]

4. Tolerability

• According to pooled data from US randomised placebo-controlled clinical studies, upper respiratory tract infection, headache, sinusitis, myalgia, tooth disorders, aggravation of diabetes mellitus and pharyngitis were reported in at least 5% of pioglitazone recipients (606 patients) [fig. 5].[56] Whether any of these adverse events were associated with the drug is not clear.

• Overall, the types of adverse events in patients undergoing combination therapy were similar to those reported in studies in which pioglitazone was given as monotherapy.[56]

• Mild to moderate hypoglycaemia has been reported in patients undergoing therapy with pioglitazone in combination with a sulphonylurea or insulin in clinical studies. Pooled data show rates of hypoglycaemia of 2 and 1%, respectively, after the addition of pioglitazone or placebo to sulphonylurea treatment.[56] Overall rates of hypoglycaemia in patients receiving insulin were 5% with the addition of placebo, 8% with pioglitazone 15 mg/day and 15% with pioglitazone 30 mg/day.[56]

• Oedema was reported more frequently with pioglitazone than with placebo in all US clinical studies.[56] Of patients who received the drug in monotherapy studies, 4.8% reported this adverse event, whereas only 1.2% of placebo recipients did so. Oedema was reported most frequently in the study in which pioglitazone was combined with insulin; the incidence of this adverse event was 8% higher with pioglitazone treatment than with placebo.[51]

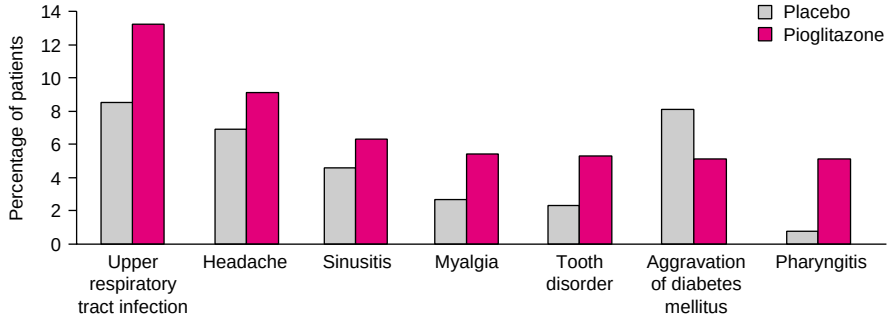


Fig. 5. Adverse events in US placebo-controlled clinical studies of pioglitazone. Overall incidences of adverse events reported at frequencies ≥5% in a study population of over 2500 patients receiving pioglitazone 7.5, 15, 35 or 45 mg/day.[56]

• Results from the US placebo-controlled study programme showed a total of 4 reports of elevated (≥3 times upper limit of normal range) serum levels of ALT after pioglitazone treatment in 1526 evaluable patients (0.26% incidence).[56] Two of 793 placebo-treated patients (0.25%) had elevated serum ALT levels. The proportion of patients withdrawn from US clinical studies because of abnormal liver function test results was below 0.12%.

• Elevation of serum creatine phosphokinase levels to more than 10 times the upper limit of the normal range was reported in 7 patients receiving pioglitazone in the US clinical studies.[56] The drug was not withdrawn in any of these patients, and all elevations resolved without incident.

• Pioglitazone appears to be well tolerated by patients aged 65 years and over, with no clinically significant differences in efficacy and tolerability having been reported between elderly and younger individuals across clinical studies.[56] The use of pioglitazone in pregnant and nursing women and in children has not been studied to date, however.

5. Pioglitazone: Current Status

Pioglitazone is an orally administered thiazolidinedione insulin sensitising antihyperglycaemic drug. It has been shown in clinical studies to reduce blood glucose levels, with beneficial effects on blood lipid profiles, and to be well tolerated as monotherapy or in combination with other antidiabetic drugs in the treatment of type 2 diabetes mellitus.

References

1. Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. Diabetes 1996 Dec; 45: 1661-9
2. Granberry MC, Fonseca VA. Insulin resistance syndrome: options for treatment. South Med J 1999 Jan; 92: 2-14
3. Lehmann JM, Moore L, Smith-Oliver TA, et al. An antidiabetic thiazoledinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPAR γ). J Biol Chem 1995 June 2; 270 (22): 12953-6
4. Strobel A, Siquier K, Zilberfarb V, et al. Effect of thiazolidinediones on expression of UCP2 and adipocyte markers in human PAZ6 adipocytes. Diabetologia 1999 May; 42: 527-33
5. Gimble JM, Robinson CE, Wu X, et al. Peroxisome proliferator-activated receptor-γ activation by thiazolidinediones induces adipogenesis in bone marrow stromal cells. Mol Pharmacol 1996 Nov; 50: 1087-94
6. Lambe KG, Tugwood JD. A human peroxisome-proliferator-activated receptor-γ is activated by inducers of adipogenesis, including thiazolidinedione drugs. Eur J Biochem 1996 Jul 1; 239: 1-7
7. Hallakou S, Doaré L, Foufelle F, et al. Pioglitazone induces in vivo adipocyte differentiation in the obese Zucker *fa/fa* rat. Diabetes 1997 Sep; 46: 1393-9
8. Dailey C, Palazuk B, Jacob C, et al. Pioglitazone (Pio) augments early steps in the insulin transduction system [abstract]. Diabetes 1993 May; 42 Suppl. 1: 116A
9. Swanson ML, Bleasdale JE. Antidiabetic agent pioglitazone increases insulin receptors on 3T3-L1 adipocytes. Drug Dev Res 1995 Jun; 35: 69-82
10. Bonini J, Hofmann C, Colca J, et al. Altered expression of insulin signaling mediators in an animal model of NIDDM is partially corrected by pioglitazone (Pio) treatment [abstract]. Diabetes 1994; 43 Suppl. 1: 186A
11. Hayakawa T, Shiraki T, Morimoto T, et al. Pioglitazone improves insulin signaling defects in skeletal muscle from Wistar fatty (*fa/fa*) rats. Biochem Biophys Res Commun 1996 Jun 14; 223: 439-44
12. Kobayashi M, Iwanishi M, Egawa K. Pioglitazone increases insulin sensitivity by activating insulin receptor kinase. Diabetes 1992 Apr; 41: 476-83
13. Sandouk T, Reda D, Hofmann C. The antidiabetic agent pioglitazone increases expression of glucose transporters in 3T3-F442A cells by increasing messenger ribonucleic acid transcript stability. Endocrinology 1993 Jul; 133: 352-9
14. Braithwaite SS, Palazuk B, Colca JR, et al. Reduced expression of hexokinase II in insulin-resistant diabetes. Diabetes 1995 Jan; 44: 43-8
15. Motojima K, Passilly P, Peters JM, et al. Expression of putative fatty acid transporter genes are regulated by peroxisome proliferator-activated receptor α and γ activators in a tissue- and inducer-specific manner. J Biol Chem 1998 Jul 3; 273: 16710-4
16. Burkey BF, Dong M, Gagen K, et al. Effects of pioglitazone on white adipose tissue remodeling in obese fa/fa Zucker rats [abstract]. Diabetes 1998 May; 47 Suppl. 1: A50
17. Hofmann C, Lorenz K, Williams D, et al. Insulin sensitization in diabetic rat liver by an antihyperglycemic agent. Metabolism 1995 Mar; 44: 384-9
18. Sugiyama Y, Taketomi S, Shimura Y, et al. Effects of pioglitazone on glucose and lipid metabolism in Wistar fatty rats. Arzneim-Forsch 1990 Mar; 40: 263-7
19. Pugazhenthi S, Khandelwal RL. Insulin action on protein phosphatase-1 activation is enhanced by the antidiabetic agent pioglitazone in cultured diabetic hepatocytes. Mol Cell Biochem 1998 May; 182: 185-91
20. Murase K, Odaka H, Suzuki M, et al. Pioglitazone time-dependently reduces tumour necrosis factor-α level in muscle and improves metabolic abnormalities in Wistar fatty rats. Diabetologia 1998 Mar; 41: 257-64
21. Sugiyama Y, Shimura Y, Ikeda H. Effects of pioglitazone on hepatic and peripheral insulin resistance in Wistar fatty rats. Arzneim-Forsch 1990 Apr; 40 Suppl. I: 436-40
22. Meglasson M, deSouza C, Yu J, et al. Effect of thiazolidinedione insulin sensitizer on growth and body composition of Zucker rats [abstract]. Diabetes 1993 May; 42 Suppl. 1: 240A
23. Hillman RM, Dailey CF, Palazuk BJ, et al. Pioglitazone hydrochloride enhances hepatic insulin responsiveness in insulin-resistant KKA^y mice and streptozotocin diabetic rats [abstract]. Diabetes 1991 May; 40 Suppl. 1: 240A
24. Kemnitz JW, Elson DF, Roecker EB, et al. Pioglitazone increases insulin sensitivity, reduces blood glucose, insulin, and lipid levels, and lowers blood pressure in obese, insulin-resistant rhesus monkeys. Diabetes 1994 Feb; 43: 204-11
25. Suzuki M, Odaka H, Sugiyama Y, et al. Effect of pioglitazone in combination with metformin on diabetes and obesity in

Wistar fatty rats [abstract]. Diabetes 1999 May; 48 Suppl. 1: A454
26. Yamasaki Y, Kawamori R, Wasada T, et al. Pioglitazone (AD-4833) ameliorates insulin resistance in patients with NIDDM. Tohoku J Exp Med 1997 Nov; 183: 173-83
27. Kawamori R, Matsuhisa M, Kinoshita J. Pioglitazone enhances splanchnic glucose uptake as well as peripheral glucose uptake in non-insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 1998 Jul; 41: 35-43
28. Kaufman LN, Peterson MM, DeGrange LM. Pioglitazone attenuates diet-induced hypertension in rats. Metabolism 1995 Sep; 44: 1105-9
29. Lardinois CK, Grinsell J, Michaels JR, et al. Pioglitazone attenuates basal and postprandial insulin concentrations and decreases blood pressure in spontaneously hypertensive rats [abstract]. Am J Hypertens 1994 Apr; 7 (Part 2): 53A
30. Verma S, Bhanot S, Arikawa E, et al. Direct vasodepressor effects of pioglitazone in spontaneously hypertensive rats. Pharmacology 1998 Jan; 56: 7-16
31. Buchanan TA, Meehan WP, Jeng YY, et al. Blood pressure lowering by pioglitazone: evidence for a direct vascular effect. J Clin Invest 1995 Jul; 96: 354-60
32. Yoshimoto T, Naruse M, Nishikawa M, et al. Insulin sensitizing agent pioglitazone has antihypertensive and reno-/vasculoprotective effects in genetically obese-diabetic rats [abstract]. Hypertension 1997 Mar; 29: 909
33. Gralinski MR, Rowse PE, Breider MA. Effects of troglitazone and pioglitazone on cytokine-mediated endothelial cell proliferation in vitro. J Cardiovasc Pharmacol 1998 Jun; 31: 909-13
34. Igarashi M, Takeda Y, Ishibashi N, et al. Pioglitazone reduces smooth muscle cell density of rat carotid arterial intima induced by balloon catheterization. Horm Metab Res 1997 Sep; 29: 444-9
35. Yoshimoto T, Naruse M, Naruse K, et al. Vasculo-protective effects of insulin-sensitizing agent pioglitazone in neointimal thickening and chronic hypertension [abstract]. J Hypertens 1998 Jun; 16 Suppl. 2: S153
36. Sato J, Arai K, Inamura T, et al. Effect of pioglitazone on atherosclerosis [abstract]. Diabetologia 1997 Jun; 40 Suppl. 1: A433
37. Suzuki M, Odaka H, Ikeda H. Pioglitazone, a new hypoglycemic agent, retards the development of diabetic nephropathy in Wistar fatty rats [abstract]. 15th International Diabetes Federation Congress 1994 Nov: Kobe, Japan, 421
38. Towns R, Kostyo JL, Colca JR. Pioglitazone inhibits the diabetogenic action of growth hormone, but not its ability to promote growth. Endocrinology 1994 Feb; 134: 608-13
39. Ogiwara T, Mikami H, Azuma J, et al. The pharmacokinetics of AD-4833 in elderly subjects [in Japanese]. Rinsho to Kenkyu 1997 May; 74 (5): 1307-18
40. Takeda Pharmaceuticals America Inc. Actos (pioglitazone hydrochloride) tablets. Prescribing information [online]. Available from: URL: http://www.actos.com/pi/htm [accessed 2000 May 1]
41. Crijns-Kortboyer J, Eckland D. Pioglitazone has low potential for drug interactions [abstract]. Diabetologia 1999 Aug; 42 Suppl. 1: A228
42. Yamazaki H, Suzuki M, Tane K, et al. *In vitro* inhibitory effects of troglitazone and its metabolites on drug oxidation activities of human cytochrome P450 enzymes: comparison with pioglitazone and rosiglitazone. Xenobiotica 2000; 30 (1): 61-70
43. Edwards G, Eckland D. Pharmacokinetics of pioglitazone in patients with renal impairment [abstract]. Diabetologia 1999 Aug; 48 Suppl. 1: A230
44. Ban S, Miyajima T, Tsumura Y, et al. Concomitant use of AD-4833, an insulin-resistance improver, and sulfonylureas: effects on serum concentrations of sulfonylureas [in Japanese]. Rinsho to Kenkyu 1997 May; 74 (5): 1217-26
45. Carey RA, Liu Y. Pioglitazone does not markedly alter oral contraceptive or hormone replacement therapy pharmacokinetics [abstract 405-P]. Diabetes 2000 May; 49 (100) Suppl. 1
46. Mathisen A, Geerlof J, Houser V. The effects of pioglitazone on glucose control and lipid profile in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A102-3
47. Schneider R, Lessem J, Lekich R. Pioglitazone is effective in the treatment of patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A109
48. Kaneko T, Baba S, Toyota T, et al. Clinical evaluation of an insulin-resistance improving agent, AD-4833, in patients with non-insulin-dependent diabetes mellitus (NIDDM) on diet therapy alone - a placebo-controlled double-blind clinical study. Rinsho to Kenkyu 1997; 74 (6): 1491-514
49. Egan J, Rubin C, Mathisen A. Combination therapy with pioglitazone and metformin in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A117
50. Schneider R, Egan J, Houser V. Combination therapy with pioglitazone and sulfonylurea in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A106
51. Rubin C, Egan J, Schneider R. Combination therapy with pioglitazone and insulin in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A110
52. King AB. A comparison in a clinical setting of the efficacy and side effects of three thiazolidinediones. Diabetes Care 2000 Apr; 23 (4): 557
53. Egan J, Rubin C, Mathisen A. Adding pioglitazone to metformin therapy improves the lipid profile in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A106
54. Mathisen A, Egan J, Schneider R. The effect of combination therapy with pioglitazone and sulfonylurea on the lipid profile in patients with type 2 diabetes [abstract]. Diabetes 1999 May; 48 Suppl. 1: A106
55. Kaneko T, Suzuki A, Inoue T, et al. Clinical evaluation of an insulin sensitivity enhancer, AD-4833, in combination with voglibose in patients with noninsulin-dependent diabetes mellitus - a non-blind phase III study. Rinsho to Kenkyu 1997; 74 (6): 1540-66
56. Takeda Pharmaceuticals America Inc. Actos (pioglitazone HCl): brief summary of prescribing information. Lincolnshire, IL, 1999

Correspondence: *Christopher J. Dunn*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz