Drugs for diabetes: part 3 thiazolidinediones

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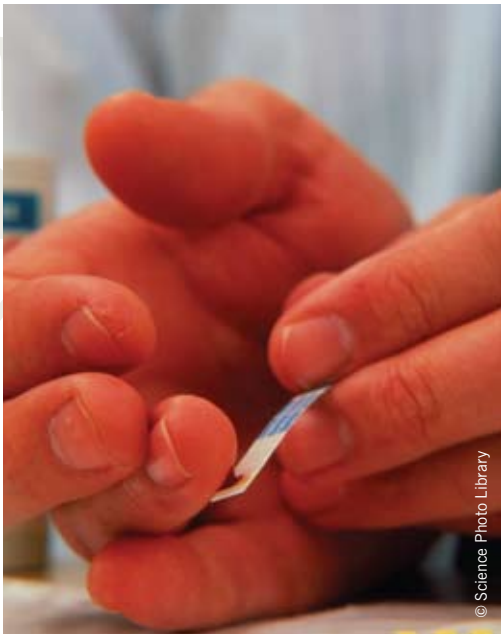
Thiazolidinediones (glitazones) are a relatively new addition to the type 2 diabetes drug armoury, but they have caused considerable controversy since they were introduced into the routine management of patients with type 2 diabetes. Until recently there were two thiazolidinediones licensed for use in the treatment of type 2 diabetes: rosiglitazone and pioglitazone, but the European Medicines Agency (EMEA) on the 23rd September 2010 removed rosiglitazone's marketing authorisation across Europe because of concerns about cardiovascular safety. There is no evidence to show a similar cardiovascular safety concern for pioglitazone, apart from increased fluid retention and reported heart failure. Pioglitazone may still have a therapeutic role in the management of selected patients.



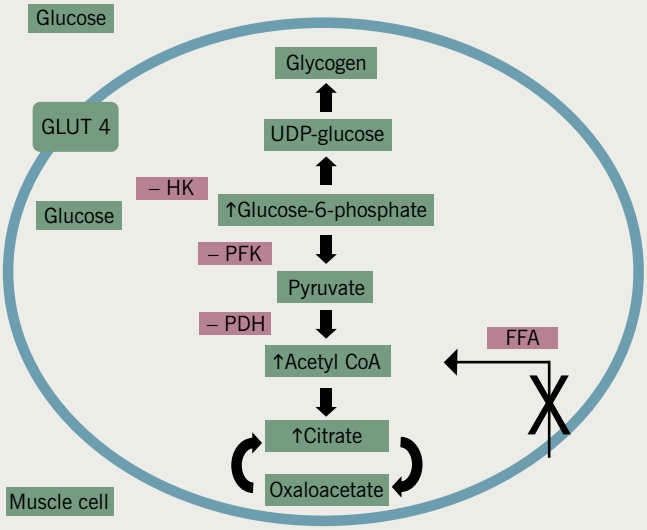
Introduction

During the past 10 to 15 years, numerous drugs have been introduced for the treatment of patients with type 2 diabetes to prevent the complications of poor glycaemic control. Two such oral drugs, rosiglitazone and pioglitazone, belong to the class of drugs called thiazolidinediones (TZDs), also known as glitazones. Both were licensed for use as monotherapy or in combination with other hypoglycaemic drugs. Through their actions on peroxisome proliferator-activated receptor (PPARγ), they improve hyperglycaemia and alter dyslipidaemia. It was hoped this would translate into cardiovascular benefits for patients taking them. Recent evidence has shown that both TZDs have different cardiovascular safety profiles, with rosiglitazone being linked to harm and pioglitazone, at worst, being neutral, although both have been shown to cause weight gain and oedema and are associated with an increased risk of heart failure. The concerns about rosiglitazone's cardiovascular safety led initially to the Medicines and Healthcare products Regulatory Agency (MHRA) issuing guidance limiting its use, but subsequently its marketing authorisation has been withdrawn, and, therefore, it is no longer available in the UK. Pioglitazone is still available for use in selected patients, but such patients should have their heart failure risk assessed before they are prescribed it.

Pharmacology

Figure 1 outlines the pharmacological action of TZDs. They increase insulin sensitivity by acting as ligands for the nuclear hormone receptor PPARγ, and regulating its transcriptional activity. PPARγ is found predominantly in adipose tissue, but it is also found in pancreatic beta cells, muscle and liver. TZDs act on PPARγ in adipocytes promoting adipogenesis, predominantly in pre-adipocytes from subcutaneous deposits where the increased transcription of transporters and enzymes involved in fatty acid uptake and lipogenesis increases the deposition of lipid in these adipocytes. This reduces hyperglycaemia by reducing concentrations of non-esterified fatty acids and triglycerides. The consequent effects on the glucose–fatty acid (Randle) cycle is to reduce the availability of fatty acids as an energy source, thereby favouring the utilisation of glucose. Additionally, TZDs increase transcription of GLUT-4 glucose transporters that directly facilitate glucose uptake. TZDs may also

Figure 1. Schematic representation of glucose–fatty acid (Randle) cycle



Oxidation of free fatty acids (FFA) results in inhibition of pyruvate dehydrogenase (PDH). Citrate inhibits phosphofructokinase (PFK). Rise in glucose-6-phosphatase inhibits hexokinase (HK). These effects reduce glucose uptake and utilisation.

X: Thiazolidinediones (TZDs) reduce FFA entering muscle cells so increasing glucose utilisation. They also increase GLUT 4 transcription so increasing glucose uptake.

Adapted from: Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963;**1**:785–9.

improve adiponectin levels, reduce adipocyte tumour necrosis factor alpha (TNF-α) and resistin production, all of which have been implicated in the pathogenesis of insulin resistance. PPARγ is also expressed by macrophages, endothelial cells and vascular smooth muscle cells, where it regulates gene expression of key proteins involved in lipid metabolism, vascular inflammation and proliferation, all of which contribute to atherogenesis. Due to these pluripotential effects, there was hope TZDs could convey cardiovascular benefit as well as glycaemic control.[1]

Pioglitazone has a half-life of 3–7 hours and is excreted in bile. It can be initiated at either 15 mg or 30 mg daily. The dose may be increased in increments up to 45 mg once daily. Pioglitazone can be used as monotherapy in patients for whom metformin is inappropriate, as dual therapy in combination with metformin, sulphonylureas and dipeptidyl peptidase-4 (DPP-4; gliptins) inhibitors, as triple therapy with two of metformin, sulphonylureas and DPP-4 inhibitors, and also with glucagon-like peptide-1 (GLP-1) receptor agonists and insulin. Commonly experienced side effects are weight gain and fluid retention.[2]

Trials of safety and efficacy

Evidence for improved glycaemic control

Both TZDs are effective at lowering glycosylated haemoglobin (HbA_{1c}) when used as monotherapy or in combination with metformin and/or sulphonylureas.[3,4] Combination therapy using doses of 4 mg and 8 mg of rosiglitazone daily lower HbA_{1c} by between 0.75% and 1.08% (8.20 and 11.80 mmol/mol). Combination therapy using doses of 15–30 mg pioglitazone daily lower HbA_{1c} by between 0.64% and 1.26% (6.99 and 13.77 mmol/mol). Convincing evidence for the durability of glycaemic control with TZDs came from A Diabetes Outcome Progression Trial (ADOPT).[5] This was a multi-centre, randomised, double-blind, controlled clinical trial designed to evaluate the durability of glycaemic control in 4,360 type 2 diabetes patients receiving monotherapy with a TZD (rosiglitazone), metformin or a sulphonylurea (glyburide). There was a 32% risk reduction of monotherapy failure with rosiglitazone compared with metformin and a 63% risk reduction of monotherapy failure with rosiglitazone versus glyburide. Rosiglitazone was associated with more weight gain and oedema than with either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycaemia than glyburide ($p<0.001$ for all comparisons). Reduced incidence of hypoglycaemia and greater gastrointestinal tolerability are consistent findings with both TZDs.[3,4]

Evidence for cardiovascular benefit

Pioglitazone

The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive) study[6] was a prospective randomised-controlled trial in 5,328 patients with type 2 diabetes who had evidence of macrovascular disease. Patients were assigned to oral pioglitazone (n=2,605) or matching placebo (n=2,633), to be taken in addition to their glucose-lowering drugs and other medications. The primary end point was the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The results of this study showed that pioglitazone non-significantly reduced the risk of the composite primary end point while significantly reducing the main secondary end point. A subgroup analysis from the PROactive trial suggested a reduction in fatal and non-fatal myocardial infarction (MI) in the subgroup with previous MI (n=2,445, hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.52–0.99, p=0.045; number needed to treat [NNT]=51, 95% CI 26–2,634).[7] In patients with previous stroke (n=984), subgroup analysis showed that pioglitazone reduced fatal or non-fatal stroke (HR 0.53, 95% CI 0.34–0.85, p=0.0085; NNT=21, 95% CI 12–75), while there was no effect on stroke risk in patients with no history of prior stroke (HR 1.06, 95% CI 0.73–1.52, p=0.767).[8]

A further meta-analysis of 84 published and 10 unpublished trials of pioglitazone compared with placebo or other therapy, and excluding the PROactive trial, reported a reduction of all-cause mortality with pioglitazone (odds ratio [OR] 0.30, 95% CI 0.14–0.63, $p<0.05$),[9] but no significant effect on non-fatal coronary events. A further meta-analysis with 16,390 patients

found a reduction in the primary composite end point (death, MI or stroke) with pioglitazone compared with control (HR 0.82, 95% CI 0.72–0.94, p=0.05).[10] While oedema, weight gain and heart failure were increased in patients in these trials, no increase in mortality from heart failure was observed. In summary, these studies and meta-analyses showed no long-term cardiovascular concerns regarding the use of pioglitazone with there being a suggestion of benefit in certain patient subgroups.

Rosiglitazone

In the last few years several meta-analyses have raised concerns about the cardiovascular safety of rosiglitazone therapy in patients with type 2 diabetes mellitus.[11-13] A Cochrane systematic review[3] of some of these data reported insufficient evidence to draw conclusions on the effect of rosiglitazone on outcomes such as cardiovascular mortality or morbidity. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial[14] was a prospective open-label non-inferiority trial where 4,447 people with type 2 diabetes were randomised to rosiglitazone-based therapy versus combination therapy with metformin and sulphonylurea. Cardiovascular hospitalisation or death was experienced by 321 patients in the rosiglitazone group versus 323 in the control group (HR 0.99, 95% CI 0.85–1.16). The study was powered to exclude a 20% or greater excess risk of cardiovascular disease with rosiglitazone. The overall event rate in the study was lower than anticipated in the study protocol power calculation, meaning the trial had less statistical power than planned. Nonetheless, the authors reported that the CI for the primary end point HR excluded the predefined 20% excess risk; therefore, it is not known whether rosiglitazone could be associated with an excess risk smaller than 20%. In this study the HR for MI was elevated, but non-significantly, at 1.14 (95% CI 0.80–1.63), while the HR for stroke was 0.72 (95% CI 0.49–1.06). Subgroup analyses of the primary end point suggested a possible non-statistically significant increase in cardiovascular events with rosiglitazone in patients with previous ischaemic heart disease (HR 1.26, 95% CI 0.95–1.68, p=0.055).

The RECORD data allied to that of the meta-analyses led the MHRA to issue the following cardiovascular restrictions:[15]

- Rosiglitazone must not be used in patients with current or previous heart failure and in patients with acute coronary syndrome
- The use of rosiglitazone is not recommended in patients with ischaemic heart disease or peripheral arterial disease
- Rosiglitazone and insulin should only be used together in exceptional cases and under close supervision.

This guidance has been superceded with the EMEA suspending the marketing authorisation across Europe. The EMEA initiated a further review of rosiglitazone following the availability of data from new studies.[16,17] The accumulated data concluded that rosiglitazone was associated with an increased cardiovascular risk compared with both placebo and with pioglitazone. In view of the restrictions already in place on the use of rosiglitazone, it was felt that there were no additional measures that could mitigate the cardiovascular risk.

Differences in cardiovascular outcomes between pioglitazone and rosiglitazone: are lipids the explanation?

The cardiovascular safety data for pioglitazone suggest a protective function in some cardiovascular subgroups. The data for rosiglitazone are suggestive of harm. The reason for the difference in outcomes may be due to the different effects both TZDs have on lipids. Goldberg *et al.*[18] conducted a randomised, prospective, multi-centre, double-blind study comparing the effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidaemia. A total of 802 patients were randomised to 24 weeks' treatment with either TZD: 360 were randomised to the pioglitazone group and 366 to the rosiglitazone group. No other glucose or lipid-lowering therapies were allowed, including statins. The effect on HbA_{1c} was similar at 24 weeks in both groups. The primary end point was effect on fasting triglyceride (TG) levels. By week four there was a significant reduction in TG values in the pioglitazone group, but a significant increase in TG in the rosiglitazone group. The values in both groups decreased over the remainder of the study but remained significantly lower with pioglitazone at each visit. At 24 weeks the mean change in TG level in the pioglitazone group was –51.9 ± 7.8 mg/dL (–12% change, p<0.001), while it was +13.1 ± 7.8 mg/dL (+14.9% change) in the rosiglitazone group. High-density lipoprotein (HDL)-cholesterol increased in both groups, but pioglitazone values (mean change ± standard error of mean [SEM]: +5.2 ± 0.5 mg/dL, +14%, p<0.001) were significantly higher than those seen with rosiglitazone (mean change ± SEM: +2.4 ± 0.5 mg/dL, +7.8%). Low-density lipoprotein (LDL)-cholesterol increased gradually with both treatments over 24 weeks. LDL particle size increased in both groups, considered a lower cardiovascular risk feature than smaller particles, but particle size was increased significantly more with pioglitazone (p<0.005). These differences could explain the different cardiovascular profiles of the two TZDs.

Table 1. Risk factors for heart failure in patients treated with thiazolidinediones

- History of heart failure
- History of myocardial infarction or symptomatic coronary artery disease
- High blood pressure
- Left ventricular hypertrophy
- Significant aortic or mitral valve disease
- Elderly (>70 years)
- Duration of diabetes >10 years
- Pre-existing oedema or treated with loop diuretics
- Development of oedema or weight gain with thiazolidinedione
- Thiazolidinedione use with insulin
- Chronic renal failure

Thiazolidinedione associated heart failure

Fluid retention manifest as peripheral oedema occurs in 4% to 6% of patients treated with TZDs. When TZDs are used alongside insulin the incidence of oedema is increased to approximately 13%. The reasons for fluid retention and oedema are multi-factorial.[19] There is an increase in plasma volume due to a reduction in renal excretion of sodium and an

increase in sodium and free water retention. TZDs may also synergistically act with insulin to cause arterial vasodilatation, leading to sodium re-absorption with a subsequent increase in extracellular volume, thereby resulting in pedal oedema. Increased sympathetic nervous system activation, alterations of interstitial ion transport, alterations in endothelial permeability and PPARγ mediated expression of vascular permeability growth factor represent mechanisms for oedema with TZDs. The peripheral oedema and fluid retention resulting in an increased plasma volume appear to be the main culprits, either alone or superimposed on pre-existing heart disease, that results in the congestive heart failure (CHF) associated with TZD use. A meta-analysis of TZD studies found an increased risk of CHF with all TZDs when compared with placebo or other diabetes medications, with an overall relative risk (RR) of 1.72 (95% CI 1.21–2.42). In this meta-analysis the RR was higher for rosiglitazone (RR 2.18, 95% CI 1.44–3.32) than for pioglitazone (RR 1.32, 95% CI 1.04–1.68).[20] Despite the increase in CHF with TZDs this meta-analysis and other studies have shown there is no difference in mortality due to heart failure between TZD and placebo or comparator.[21]

Nonetheless, pioglitazone should not be used in patients with known heart failure. In patients who are not known to have established heart disease but who have one or more risk factors for CHF (**table 1**), it is advisable to start with low doses and to increase the dose slowly if required, while being vigilant for any signs of excessive weight gain, peripheral oedema or CHF.[22]

Discussion

Pioglitazone is the only remaining TZD licensed for use in the treatment of type 2 diabetes in the UK, following the marketing authorisation for rosiglitazone being withdrawn across Europe. It can offer effective and durable glycaemic control with fewer gastrointestinal side effects than metformin, and it is less likely to cause hypoglycaemia than sulphonylureas. It may have a use in selected patients, but care should be taken in assessing suitable patients as it is associated with weight gain and oedema and an increased risk of heart failure

Conflict of interest

MF has received speaker's honoraria and served on advisory panels for GlaxoSmithKline and Takeda. GM and DM: none declared.

Key messages

- Pioglitazone is the only thiazolidinedione still available for use in the UK following the suspension of marketing authorisation for rosiglitazone in Europe because of concerns about cardiovascular safety
- Different effects on lipids may explain why there are fewer concerns about the cardiovascular safety of pioglitazone
- Before prescribing pioglitazone assess each patient's heart failure risk and avoid in known heart failure
- Warn patients of the risk of oedema. If oedema occurs advise them to seek medical advice. Clinicians should withdraw pioglitazone and treat and investigate the heart failure conventionally

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