Professor Chisholm has received research funding for preclinical studies on thiazolidinediones and has given lectures for and participated in advisory boards for both Eli Lilly and GlaxoSmithKline, marketers of pioglitazone and rosiglitazone. He has no beneficial interest and does not receive consultancy payments from either company other than for lectures and advisory board meetings.

Self-test questions

The following statements are either true or false (answers on page 79)

5. Treatment with thiazolidinediones leads to weight reduction in patients with type 2 diabetes.
6. Haemoglobin concentrations may fall during treatment with thiazolidinediones.

Experimental and clinical pharmacology

Clinical indications for thiazolidinediones

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Summary

Undertreatment of hyperglycaemia in type 2 diabetes is a major therapeutic problem. This is partly because reduced insulin sensitivity and beta cell failure become resistant to current therapies. The thiazolidinediones are a new class of drugs that improve insulin sensitivity. However, large-scale clinical trials are needed to assess their clinical roles and whether they have microvascular protective effects beyond those associated with lowering blood glucose. Trials with clinical end-points are also required to determine if thiazolidinediones reduce macrovascular disease. Thiazolidinediones can cause delayed-onset hypoglycaemia, especially in combination with other oral hypoglycaemic drugs, weight gain and fluid retention. The fluid retention may precipitate heart failure so careful monitoring of weight gain and peripheral oedema is required.

Key words: diabetes, hypoglycaemic drugs, pioglitazone, rosiglitazone.

(Aust Prescr 2004;27:70–4)

Introduction

Lifestyle changes including weight loss and increased activity are the primary recommendations for treatment of type 2 diabetes. However, because of the progressive nature of the disease, the treatment of type 2 diabetes usually requires the stepwise introduction of oral hypoglycaemic drugs followed by insulin.[1] Despite this approach less than 10% of patients with type 2 diabetes maintain their concentration of glycated haemoglobin (HbA1c) below 7%, which is still about two standard deviations above the upper limit of the normal range. The reasons for this are complex and include factors relating to organisations, doctors, patients and deficiencies in drug efficacy. These may arise from a delay in the translation of new guidelines into clinical practice, patient resistance to starting insulin and secondary failure of existing oral hypoglycaemic drugs.

The thiazolidinediones are a recent addition to the list of hypoglycaemic drugs (Table 1). Rosiglitazone and pioglitazone are now listed on the Australian Pharmaceutical Benefits Scheme (PBS) for the treatment of type 2 diabetes.

Mechanism of action

Thiazolidinediones do not stimulate insulin secretion. They act by improving insulin sensitivity via activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ). There is an increase in glucose utilisation by skeletal muscle and fat cells, increased uptake of free fatty acids and reduced lipolysis by fat cells, and to possibly a lesser extent a reduction in hepatic gluconeogenesis. For fat cells the ratio of adipogenesis to apoptosis is also differentially altered favouring apoptosis of larger insulin-resistant cells and the proliferation of smaller insulin-sensitive adipocytes. This is accompanied by a shift in the distribution of fat from central to peripheral depots.

Glycaemic control – response, onset and duration of action

Thiazolidinediones progressively reduce concentrations of blood glucose. The HbA1c falls by 0.5–1.5% over one to three months. Maximal glucose-lowering effects may not be seen for up to three months and therefore dose adjustments prior to this time should be undertaken with caution.

The hypoglycaemic effects of pioglitazone 15–45 mg daily are similar to those of rosiglitazone 4–8 mg daily. The thiazolidinediones produce a wider response in HbA1c concentrations in comparison to other oral hypoglycaemic drugs. It is not possible to differentiate 'good' from 'bad' responders prospectively but, in general, the reduction in HbA1c is greater when thiazolidinediones are used in combination with other drugs. There is also some evidence to suggest that obese patients respond better than those with a body mass index close to normal. Defining the proportion of patients who respond to a thiazolidinedione is a difficult question to answer because there is no clear definition of a 'responder'. The context of a response therefore could vary in the setting of mono-, dual or triple therapy, however, possibly up to 30% of patients may not respond with a decrease in HbA1c concentrations.

A major question is whether the glycaemic response to thiazolidinediones is maintained longer than with other oral hypoglycaemic drugs. So far, studies up to four years in duration have not shown a delayed increase in HbA1c. It will require at least another four years before it is clear whether or not secondary failure occurs with thiazolidinediones as it does with other oral hypoglycaemic drugs.

Adverse effects

The thiazolidinediones have effects in many different tissues. As only limited information is available on their long-term use, significant adverse effects may yet emerge. Monotherapy with thiazolidinediones is not associated with hypoglycaemia, but clinical hypoglycaemia has been reported when they are used in combination therapy. Hypoglycaemia may occur many weeks after starting a thiazolidinedione because of the slow onset of action.

Troglitazone, the first member of the class, was withdrawn as a consequence of liver failure. Hepatotoxicity has not been a problem with pioglitazone and rosiglitazone although regular monitoring of liver function is still recommended.

The main adverse effects of thiazolidinediones are weight gain of 1–4 kg after six months of treatment, fluid retention and dilutional anaemia. Increases in weight reflect fluid retention and an increase in peripheral fat mass (albeit with a concurrent decrease in central fat). The fluid retention may be due to increased endothelial cell permeability or a renal effect of thiazolidinediones, but a local vasodilatory action cannot be excluded. Oedema may occur more frequently in patients with a good glycaemic response to thiazolidinediones, especially those who are taking insulin. It is also more likely to be noticed in patients taking medications that promote oedema such as dihydropyridine calcium channel blockers. Thiazolidinediones can be used in patients with renal impairment as long as fluid overload is not an issue.

Heart failure

The most dangerous adverse effect of thiazolidinediones is fluid retention leading to congestive cardiac failure. Some degree of peripheral oedema occurs in 5–15% of patients and 2–3% develop cardiac failure. A recent retrospective cohort study has shown that the use of thiazolidinediones was associated with an approximately 70% increase in the relative risk of developing heart failure.[2] In that study, the adjusted estimated incidence of heart failure (defined as a hospitalisation or outpatient visit

Table 1

Comparison of oral hypoglycaemic drugs available in Australia

Drug class	Preparations available	Mechanism of action	Pharmaceutical Benefits Scheme listing
Thiazolidinediones	rosiglitazone pioglitazone	increase insulin sensitivity	authority required
Biguanides	metformin	reduce hepatic gluconeogenesis	unrestricted benefit
Sulfonylureas	glibenclamide gliclazide gliclazide MR glimepiride glipizide	increase pancreatic insulin secretion	unrestricted benefit
Meglitinides	repaglinide	increase pancreatic insulin secretion	not listed
α-glycosidase inhibitors	acarbose	delay absorption of complex carbohydrates	authority required

with a diagnosis of heart failure) was 8.2% for thiazolidinedione-treated patients and 5.3% for the control group after 40 months of exposure.

A joint consensus statement regarding thiazolidinedione use, fluid retention and heart failure has been released by the American Heart Association and the American Diabetes Association.[3] The following factors are associated with an increased risk of developing heart failure:

- history of heart failure (systolic or diastolic)
- history of prior myocardial infarction or symptomatic heart failure
- hypertension
- left ventricular hypertrophy
- significant aortic or mitral valve disease
- advanced age (over 70 years)
- long-standing diabetes (over 10 years)
- pre-existing oedema or current treatment with loop diuretics
- development of weight gain or oedema on thiazolidinedione therapy
- insulin co-administration
- chronic renal failure.

Thiazolidinediones are therefore contraindicated in patients with moderate to severe symptoms or signs of angina or heart failure during daily activities or at rest (New York Heart Association (NYHA) class III or IV cardiac functional status). For patients in the class I or II NYHA categories, thiazolidinediones can probably be prescribed with extreme caution. It is recommended that patients start with the lowest doses of thiazolidinediones and be carefully observed for fluid retention. The same caution should also apply to patients who do not have symptoms or signs of heart failure, but who have had an echocardiogram revealing impaired ventricular function.

Drug interactions

Pioglitazone is partially metabolised by cytochrome P450 3A4 and rosiglitazone is predominantly metabolised by P450 2C8. A number of drugs used in everyday clinical practice modulate the activity of the P450 3A4 enzyme and gemfibrozil has been reported to inhibit the P450 2C8 enzyme resulting in increased concentrations of rosiglitazone. However, no clinical syndromes have yet been reported as a result of drug interactions that could potentially alter the metabolism of the thiazolidinediones.

Clinical indications for the treatment of type 2 diabetes

In the absence of cost and regulatory considerations, thiazolidinediones could potentially be used in:

- monotherapy
- dual therapy with either a sulfonylurea or metformin
- triple therapy in combination with both a sulfonylurea and metformin
- combination with insulin.

Current PBS regulations do not allow all of these options.

Monotherapy

When used alone, pioglitazone and rosiglitazone are effective at reducing concentrations of HbA1c and fasting blood glucose in adults with type 2 diabetes. These effects are similar to those of other available oral hypoglycaemic agents.

Combined therapy with other oral drugs

The advantages of adding thiazolidinediones are mainly theoretical and include the preservation of β-cell function and hence secondary failure, and possibly cardiovascular protection. These effects remain to be rigorously tested in large prospective clinical studies.

For patients on monotherapy with either a sulfonylurea or metformin, the addition of a thiazolidinedione produces a further significant decrease in HbA1c and fasting blood glucose.[4] However, there is little evidence to suggest that this approach will provide better short-term glycaemic control than the combination of metformin and a sulfonylurea.

The use of thiazolidinediones under the PBS is limited to the combination with either metformin or a sulfonylurea. Patients must have an intolerance or contraindication to either metformin or a sulfonylurea to qualify for treatment with thiazolidinediones. As intolerance and contraindications are more common with metformin than with sulfonylureas, the main use of thiazolidinediones in Australia is likely to be in combination with a sulfonylurea.

In contrast to the PBS listing, the main use of thiazolidinediones so far in Australia has been in combination with both metformin and a sulfonylurea as part of schemes sponsored by the manufacturers of pioglitazone and rosiglitazone. This triple therapy has evolved for two reasons. Firstly, it is now common practice to combine metformin with a sulfonylurea at an early stage of treatment of diabetes and secondly, patients are reluctant to start insulin when metformin and a sulfonylurea no longer control their blood glucose. Clinical studies have suggested that the addition of a thiazolidinedione to the combination of metformin and a sulfonylurea decreases HbA1c levels by 0.6–1.8% over 6–36 months. In one placebo-controlled study of patients already receiving a sulfonylurea and metformin the addition of rosiglitazone resulted in a greater reduction in HbA1c levels (–0.9 v. +0.1%) and a larger proportion of patients achieving a HbA1c < 7% (42 v. 14%) after 24 weeks.[5]

The possible benefits of using a thiazolidinedione to delay starting insulin are less clear. One study randomised patients with secondary failure receiving both metformin and insulin secretagogues to the addition of pioglitazone or bedtime NPH insulin. After 16 weeks HbA1c levels were lowered to a similar degree with pioglitazone (–1.9%) or insulin (–1.5%) but hypoglycaemia was less common in patients treated with pioglitazone.[6]

Combined therapy with insulin

Thiazolidinediones have been used in combination with insulin. They lower HbA1c concentrations by 0.6–1.2% compared with placebo plus insulin. At present the PBS only lists the combination of pioglitazone and insulin. The combination of insulin, metformin (to improve hepatic insulin sensitivity) and a thiazolidinedione (to improve peripheral insulin sensitivity) has also been suggested as a useful approach to improve glucose metabolism in type 2 diabetes.

Non-hypoglycaemic effects and emerging indications

The established glycaemic, 'non-hypoglycaemic' and emerging indications for the use of thiazolidinediones are summarised in Table 2. Many of these emerging indications will require extensive research before they can be accepted into practice.

How to prescribe the thiazolidinediones

At present the available preparations are:

- pioglitazone 15, 30 and 45 mg tablets (daily dose)
- rosiglitazone 4 and 8 mg tablets (daily or twice-daily dose).

An authority prescription is required if the drugs are prescribed under the PBS. The PBS indications are restricted.

Approved indications under the PBS

Pioglitazone or rosiglitazone can be initiated as dual therapy with either metformin or a sulfonylurea. There must be a contraindication to or intolerance of therapy with metformin plus sulfonylureas and the patient's blood glucose concentrations must have been inadequately controlled. (Inadequate control is defined as HbA1c > 7%, despite diet, exercise and maximal-tolerated doses of metformin or sulfonylureas.)

Pioglitazone can also be initiated in combination with insulin, in patients with type 2 diabetes whose blood glucose concentrations are inadequately controlled by insulin alone. Inadequate control is defined as HbA1c > 7%, despite concomitant use of insulin and oral anti-diabetic drugs.

The initial application for an authority prescription requires the HbA1c concentration, the date of measurement and the reason for the contraindication or intolerance to either metformin or sulfonylureas. For repeat prescriptions the HbA1c should not have deteriorated since starting treatment and it should be under 8.5% on at least two occasions within 10 months of starting treatment. Pathology reports, from accredited laboratories, must be available with patients' records for audit by the Health Insurance Commission.

Table 2

Potential scope for thiazolidinedione use

Indication	Rationale
Prevention of type 2 diabetes	Thiazolidinediones improve insulin sensitivity and may preserve β-cell function. Trials are in progress to assess the effectiveness of thiazolidinediones in preventing the onset of type 2 diabetes.
Metabolic syndrome/insulin resistant states	A decrease in insulin resistance ameliorates the metabolic syndrome and its associations such as dyslipidaemia (see below), hypertension and microalbuminuria.
Dyslipidaemia	Thiazolidinediones raise concentrations of high density lipoprotein, with pioglitazone having the greatest effects. Pioglitazone also reduces triglycerides. Rosiglitazone raises low density lipoprotein (LDL) concentrations, but this is associated with a shift from small dense to large buoyant LDL particles that are thought to be less atherogenic. Whether this effect negates the increased cardiovascular risk associated with a raised LDL is unknown. Pioglitazone does not significantly increase LDL concentrations.
Cardiovascular protection	PPARγ receptors are present in vascular tissues. Thiazolidinediones may have protective effects on small and large blood vessels beyond those expected from glucose-lowering effects alone. Long-term studies are currently evaluating this possibility.
Polycystic ovary syndrome	Thiazolidinediones induce ovulation, and decrease insulin and androgen concentrations.
Non-alcoholic steatohepatitis	Improvements in liver function tests and liver biopsy findings have been reported.
Lipodystrophy (HIV and non-HIV related)	Thiazolidinediones alter fat distribution in non-HIV lipodystrophy. Although there is some evidence supporting the use of thiazolidinediones in HIV patients with lipodystrophy related to highly active antiretroviral use, this approach has not been supported by a recent randomised, double-blind clinical trial.
Effects on tumour growth	Thiazolidinediones have been shown to have both inhibitory and stimulatory effects in a variety of experimental models of tumour growth. As yet there have been no clinical studies.

Practice tips for prescribing the thiazolidinediones

- The maximal hypoglycaemic effects of thiazolidinediones may not be seen for up to three months; dose changes prior to this time are not recommended.
- Be wary of delayed onset hypoglycaemia.
- Thiazolidinediones are contraindicated if the patient's alanine aminotransferase concentrations are more than 2.5 times the upper limit of normal. The product information recommends that liver function is checked when starting treatment, every second month for the first year and then periodically thereafter.
- Thiazolidinediones should not be taken by women who are pregnant or breastfeeding. Women with polycystic ovary syndrome should be warned that thiazolidinediones may induce ovulation. They may need contraception.
- Not all patients will respond to thiazolidinedione therapy with a decrease in HbA1c.
- Guidelines for starting a thiazolidinedione and stopping metformin or a sulfonylurea have been prepared by the Australian Diabetes Society.

Conclusion

Deciding when a thiazolidinedione is appropriate requires consideration of their advantages and disadvantages. Potentially, the thiazolidinediones could be useful in the treatment of type 2 diabetes as they act to improve insulin sensitivity. However, the clinical evidence supporting their use is still very limited.[7] There is no current evidence to suggest that the glucose-lowering actions of thiazolidinediones are greater than those of other oral hypoglycaemic drugs. Thiazolidinediones might be shown to preserve β-cell function, alleviate many of the components of the metabolic syndrome/insulin resistance states, and offer cardiovascular protection. Both beneficial and adverse effects remain to be tested in large, long-term prospective clinical studies. Under current PBS criteria the main use of thiazolidinediones in Australia will most likely be in patients already taking a sulfonylurea who have an intolerance of or contraindication to metformin.

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Both Dr MacIsaac and Professor Jerums have received speakers' fees and travel support from Eli Lilly and GlaxoSmithKline. Professor Jerums has also served on the advisory board for GlaxoSmithKline.

Self-test questions

The following statements are either true or false (answers on page 79)

7. The combination of insulin and a thiazolidinedione may precipitate heart failure.
8. The maximum fall in blood glucose concentrations occurs approximately one week after starting a thiazolidinedione.

More information about the listing of pioglitazone and rosiglitazone in the Schedule of Pharmaceutical Benefits is available on the National Prescribing Service RADAR web site at

http://www.npsradar.org.au/articles/pioglitazone.php
http://www.npsradar.org.au/articles/rosiglitazone.php