Getting to know the glitazones

The 'glitazones' are a new class of compounds for the treatment of type 2 diabetes. They exert their glucose-lowering effect by improving the sensitivity of the peripheral tissues to insulin. They are active alone and in combination with other oral antidiabetic agents and with insulin.

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Although the combination of dietary modification with calorie restriction and exercise is the cornerstone of therapy for type 2 diabetes, more than 90% of patients with this condition ultimately require drug treatment, with most needing combination therapy with two or more agents. Yet, despite the soaring incidence of type 2 diabetes since the 1950s, there has been a distinct lack of progress in the development of new therapeutic modalities for its treatment. The addition of the thiazolidinediones (or 'glitazones') – a completely new therapeutic class – to the armamentarium of available oral hypoglycaemic agents has ushered in a new era of diabetes management.

The metabolic syndrome: insulin resistance

It is thought that a central feature of the deranged metabolism that leads to type 2 diabetes and its associated clinical phenomena is the accumulation of triglycerides and other fatty acids in muscle, liver and pancreatic islets, leading to insulin resistance and impaired insulin secretion. This state is known as the 'metabolic syndrome' (also known as the insulin resistance syndrome, or Syndrome X).

The tissue accumulation of triglycerides and fatty acids is consequent upon high concentrations of circulating fatty acids. This occurs with reduced physical activity, excess dietary fat and increased fatty acid release from an expanded mass of intra-abdominal adipose tissue, promoting hepatic triglyceride synthesis and very low density lipoprotein (VLDL) output. (Visceral fat [i.e. intra-abdominal fat] is metabolically different from nonvisceral fat [i.e. peripheral or subcutaneous fat].)

Type 2 diabetes

Type 2 diabetes is characterised by progressive

IN SUMMARY

- **The glitazones are a new class compounds for the treatment of type 2 diabetes that exert their glucose-lowering effect by improving the sensitivity of peripheral tissues to insulin.**
- **A large part of their action appears to be mediated through changes in body fat and its distribution; they also affect adipocyte hormone production (particularly adiponectin), which may result in additional favourable biological effects.**
- **Rosiglitazone and pioglitazone are listed on the PBS for use in patients with type 2 diabetes as monotherapy and in combination with sufonylureas, metformin, or both, where blood sugar levels are not controlled with lifestyle measures.**
- **Pioglitazone is subsidised also for combination therapy with insulin.**
- **The main adverse effect of the glitazones is weight gain, and an important class effect is fluid retention, causing peripheral oedema in 3 to 5% of patients.**

β-cell secretory dysfunction in the setting of insulin resistance, which is usually present for many years before the onset of hyperglycaemia. To overcome this metabolic defect, a state of chronic hyperinsulinaemia prevails whereby the pancreatic β-cells secrete large quantities of insulin to maintain normoglycaemia.

After a variable period (usually years), the β-cells gradually fail to release sufficient insulin to ensure physiological blood glucose levels (Figure 1). When there is failure to suppress the fasting plasma glucose level below 7.0 mmol/L (and/or a 2-hour postprandial plasma glucose below 11.1 mmol/L), type 2 diabetes is said to be present. For some (often unnoticed) period before this, the fasting and/or postprandial glucose levels are high, but less than the above values, and lesser degrees of abnormal glucose metabolism exist, known as 'impaired fasting glycaemia' or 'impaired glucose tolerance'.

Insulin maintains glucose homeostasis by acting on skeletal muscle (to uptake glucose) and the liver (to suppress glucose production [gluconeogenesis]). Thus the insulin resistant state is characterised by impaired glucose uptake in muscle and increased rates of hepatic glucose output, which peaks nocturnally, and is the main contributor to morning hyperglycaemia (Figure 2).

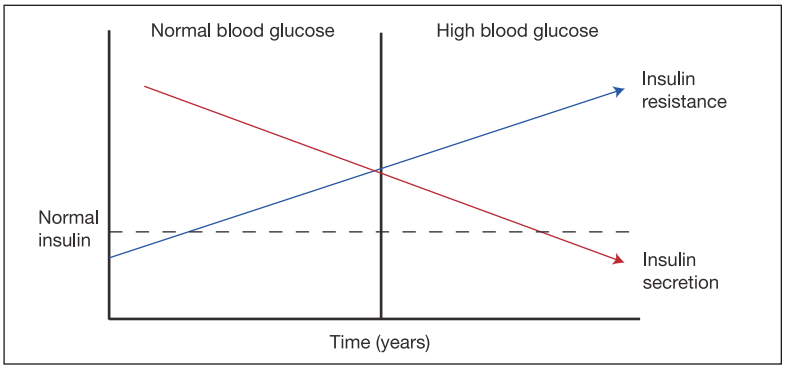

Figure 1. A schematic representation of the inverse relation between insulin resistance and insulin secretion, and the resulting impact on blood glucose levels.

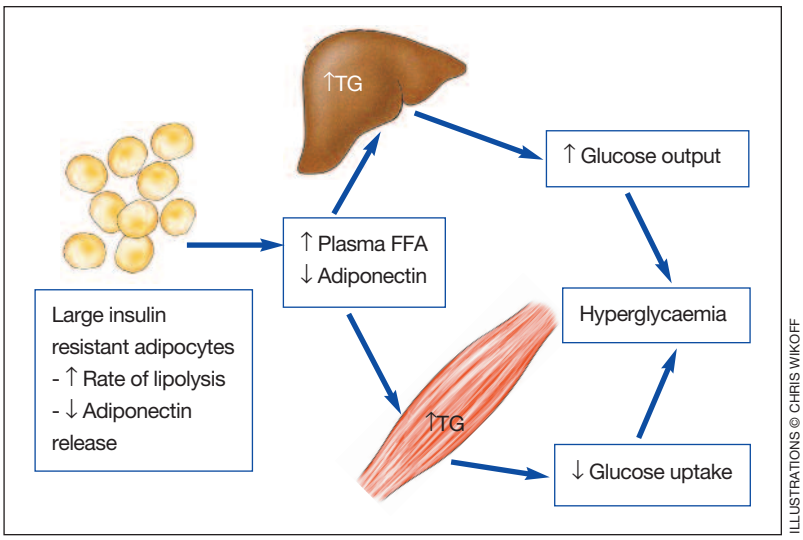

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Figure 2. Accumulation of triglycerides (TG) and surplus free fatty acids (FFA), together with reduced adiponectin, leads to insulin resistance in fat, liver and muscle. This results in defective insulin action and ultimately hyperglycaemia.

Other components of the metabolic syndrome

Besides disturbing glucose homeostasis, impairment of the normal vasodilating effect of insulin may contribute to the development of hypertension. Also, hepatic insulin resistance contributes to dyslipidaemia, characterised by:

- decreased HDL concentration
- increased triglyceride concentration
- decreased LDL particle size (smaller LDL particles are thought to be more adherent to vascular endothelium).

Other metabolic abnormalities associated with insulin resistance include:

- increased circulating concentrations of C-reactive protein (CRP) and other inflammatory mediators
- endothelial dysfunction
- reduced release of adipocyte hormones (e.g. adiponectin), which are thought to modulate fatty acid transport.

These are thought to link insulin resistance with accelerated atherogenesis and cardiovascular disease.

The preglitazone era

The pharmacological treatment of type 2 diabetes has traditionally involved the use of metformin, sulfonylureas or insulin, or a combination of any two or all of these medications. Occasionally, repaglinide (NovoNorm), which stimulates insulin secretion, and acarbose (Glucobay), which inhibits the absorption of glucose from the gut, have also been used.

Metformin

Metformin has been available in Australia for half a century. It is usually the first-line agent for patients with type 2 diabetes after the UK Prospective Diabetes Study (UKPDS) showed its benefit in reducing the incidence of cardiovascular disease in overweight patients with this condition.[1] It acts largely by reducing excessive hepatic glucose production. This is thought to mediate an 'insulin-sensitising' effect; when used with insulin, metformin may reduce the required daily injected dose by up to 20 to 30%.

In many patients gastrointestinal side effects limit metformin's use, although only 10 to 15% are unable to tolerate the drug at all. Metformin should be avoided in patients with significant renal impairment (creatinine clearance less than 50 mL/min) and in those with significant cardiac or respiratory failure, active liver disease or systemic illness, due to the risk of lactic acidosis (which is extremely rare but usually fatal).

Sulfonylureas

Sulfonylureas (including gliclazide [Diamicron, Glyade, Nidem], glipizide [Melizide, Minidiab], glibenclamide [Daonil, Glimel] and glimepiride [Amaryl, Dimirel]) have been available for several years. These 'insulin secretagogues' stimulate insulin secretion from the pancreas, thereby reducing the rise in blood glucose seen after a meal. In doing so, they can cause hypoglycaemia, which may be profound, especially in the elderly. (This is not seen with metformin when it is given alone, but metformin potentiates the hypoglycaemic action of sulfonylureas when used in combination.)

Otherwise, sulfonylureas are well tolerated, apart from the rare case of allergy to these medications (not to be confused with sulfur/sulfonamide allergy). Sulfonylureas also tend to exacerbate the hyperinsulinaemia that is a characteristic feature of insulin resistance and type 2 diabetes, and tend to increase body fat.

Insulin

Insulin is given to patients with type 2 diabetes when their glycaemic control is insufficiently maintained by the use of metformin or sulfonylureas, or both. It can be used in place of, or as a supplement to, oral therapy.

The main problems with insulin therapy are poor patient acceptance, hypoglycaemia and weight gain. Like sufonylureas, insulin adds to the burden of hyperinsulinaemia associated with the metabolic syndrome.

The glitazones

The glitazones are orally active medications that directly target insulin resistance. By sensitising the peripheral tissues (fat, skeletal muscle and liver) to insulin, they enhance its effect as a hormone (i.e. when released endogenously in response to a meal or by secretagogues), or as a drug (i.e. when given by injection), thereby reducing blood sugar levels.

The glitazones available are rosiglitazone (Avandia) and pioglitazone (Actos). Troglitazone was withdrawn from use in clinical practice in 2000 after exhibiting uncommon but serious liver toxicity; this adverse effect does not appear to be associated with the other two compounds.

There is a marked heterogeneity of patient responsiveness to the glitazones. Anecdotal data suggest that about:

- 10% of patients respond spectacularly well and require dramatic dose reduction in their other diabetic medication
- 30% respond very well
- 40% have a modest to good response
- 20% respond poorly or not at all.

Predictors of response may include the degree of abdominal, or central, obesity, with a positive correlation existing between waist circumference and response. Thus these medications are less likely to be useful in patients who are relatively lean.

It is well established that the glitazones may delay or postpone the need for insulin in many patients, although the identification of such patients is not simple.

Studies have shown that in patients with inadequate glycaemic control, the glitazones may improve the glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose to an extent comparable to that induced by metformin and sulfonylureas. They are also effective in combination with these agents and with insulin.

How they work

The precise mechanism by which the glitazones directly improve insulin sensitivity is not completely understood; however, it appears that a large part of their action is mediated through changes in body fat and its distribution.

The glitazones bind avidly to a steroid receptor (the gamma isoform of the peroxisome proliferator-activated receptor, known as PPARγ) in the cells of peripheral, but not visceral, fat. Here they promote fatty acid uptake and expansion of tissue. This reduces circulating fatty acid levels and lipid availability in the liver and muscle (Figure 3), but also increases total body fat. Some evidence suggests that the fat is redistributed in a favourable direction – i.e. from visceral to subcutaneous depots (Figure 4).[2]

The glitazones are thought also to improve insulin sensitivity by altering adipocyte hormone production (particularly adiponectin).

Beneficial nonhypoglycaemic effects

Numerous effects of the glitazones that have no direct bearing on blood sugar concentrations have been observed, including the following:[3]

- increased HDL cholesterol levels
- increased LDL cholesterol particle size (which are more buoyant, rendering them less atherogenic)
- reduced triglyceride levels
- small hypotensive effect
- reduced incidence of microalbuminuria
- decreased plasminogen activator

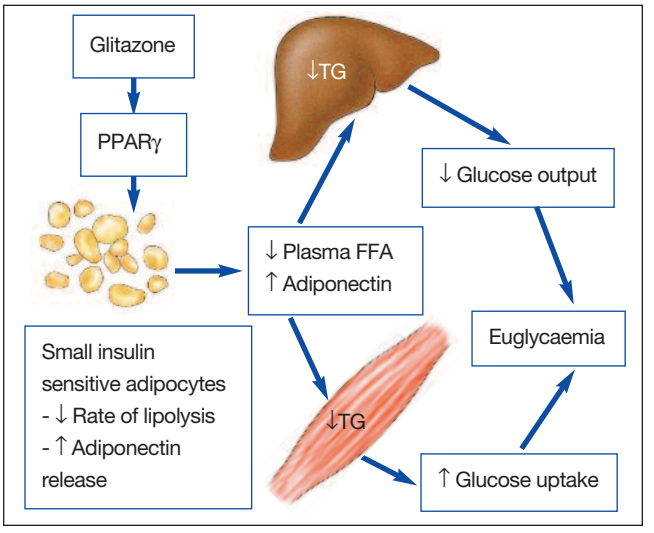

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Figure 3. PPARγ activation in adipose tissue decreases hepatic and muscle insulin resistance via reduced plasma free fatty acids (FFA). Increased fatty acid storage in subcutaneous adipocytes causes a lipid redistribution phenomenon, leading to lower circulating FFA and reduced levels of triglycerides (TG) in muscle and liver. Together with increased adiponectin levels, this results in improved insulin action and normalisation of blood sugar levels.

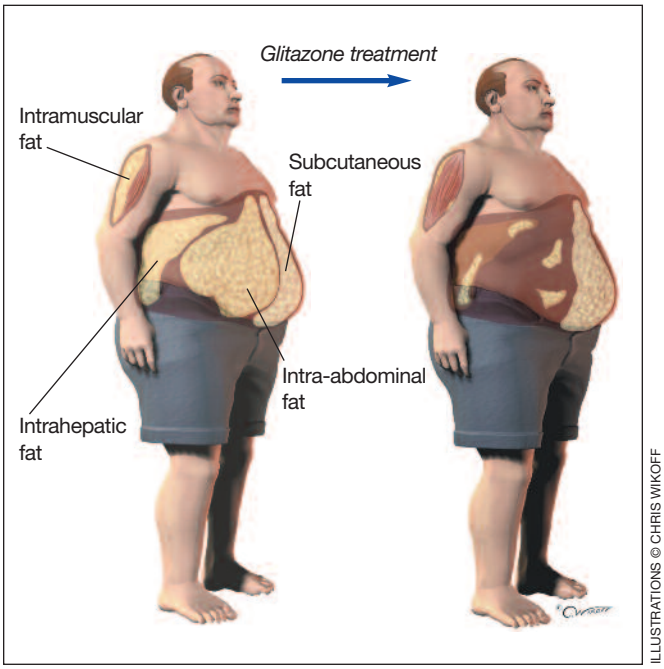

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Figure 4. Proposed effects of glitazones on fat distribution. Adapted with permission from Professor Ralph A. DeFronzo, University of Texas Health Science Centre, San Antonio, Texas, USA.

inhibitor-1 and fibrinogen levels
- vasorelaxation
- anti-inflammatory effects.[4]

Most of these effects are potentially beneficial, and many are probably due to changes in lipid metabolism or fat-cell hormones.

It must be stressed, however, that patients with dyslipidaemia or hypertension should be treated with appropriate lipid lowering or antihypertensive medication to reduce associated excess cardiovascular risk. This must be regardless of whatever salutary effect glitazone therapy has on lipid or blood pressure parameters in a given patient.

When should they be used?

Currently, rosiglitazone and pioglitazone are approved on the PBS for use in patients with type 2 diabetes as monotherapy and in combination with sulfonylureas, metformin, or both, where blood sugar levels are not controlled with lifestyle measures. Pioglitazone is also subsidised for combination therapy with insulin; it is expected that rosiglitazone will also have this indication in the near future.

Although almost all patients with type 2 diabetes are probably suitable for glitazone treatment (except those with contraindications), the medications are expensive. They are generally used as second- or third-line therapies when patients have contraindications or intolerances to metformin or sulfonylureas (Table 1).

The PBS criteria and authority requirements for the glitazones are summarised in the box on page 60; however, it is legitimate to prescribe outside these criteria (but within the indications) if the patient is willing to pay the nonsubsidised price. Off-label use for patients with insulin-resistant states but without diabetes should be avoided.

When are they not useful?

Glitazones improve insulin action and glycaemic control in patients with diabetes

Table 1. Sulfonylureas and metformin: contraindications and intolerances*

Sulfonylureas

Contraindications
- Allergy to sulfonylureas

Common reasons for intolerance
- Hypoglycaemia
- Rash

Metformin

Contraindications
- Heart failure
- Recent myocardial infarction
- Respiratory failure
- Severe infection or trauma
- Dehydration
- Renal impairment
- Hepatic impairment

Common reasons for intolerance
- Nausea
- Diarrhoea

* Not exhaustive.

Summary of PBS criteria for the glitazones

The PBS listing requires that both rosiglitazone and pioglitazone be used only in the circumstances summarised below and in Figures A and B.

- When adding metformin to a patient inadequately controlled (despite diet and exercise) on a sulfonylurea is not appropriate (e.g. due to adverse effects) or contraindicated (see Table 1) – in this case a glitazone could be added to a sulfonylurea.
- When adding a sulfonylurea to a patient inadequately controlled (despite diet and exercise) on metformin is not appropriate (see Table 1) or contraindicated (e.g. risk of falls due to hypoglycaemia in the elderly) – in this case a glitazone might be added to metformin.
- When up-titration of either metformin or sulfonylurea to improve glycaemic control in a patient taking both agents produces intolerance to one of them (e.g. gastrointestinal side effects on high-dose metformin) – in this case the offending drug might be withdrawn (slowly, especially if a sulfonylurea) and replaced by a glitazone.

Note: In the above cases, insulin could be used as an alternative to the glitazone (i.e. adding a glitazone is not the only option).

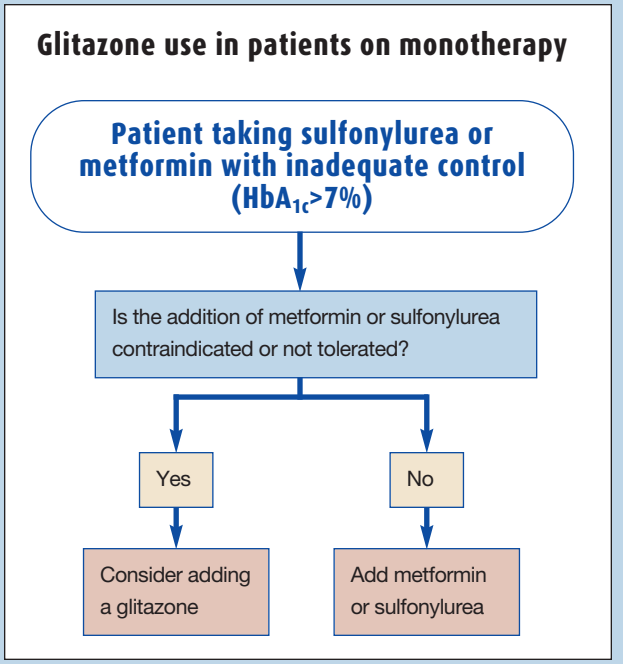

Figure A. PBS authority use of a glitazone in patients on metformin or sulfonylurea monotherapy.

Also, for pioglitazone:

- In patients taking insulin and metformin and/or a sulfonylurea, for pioglitazone to be prescribed under the PBS, both metformin and the sulfonylurea must be ceased or intended to be ceased, citing reasons for intolerance or contraindications to the conventional agents. Most patients on insulin would be on metformin only, in which case this is usually the drug that should be replaced by pioglitazone in a patient on insulin (if deemed appropriate by the clinician).

Authority requirements

The first authority prescription for the glitazones allows five months' therapy and there is automatic approval for a second five-month supply. For further authority to then be granted, it must be shown that at least two successive HbA_{1c} levels have fallen consecutively from the initial value (which had to be >7.0%) during the four-month period preceding the initial application.

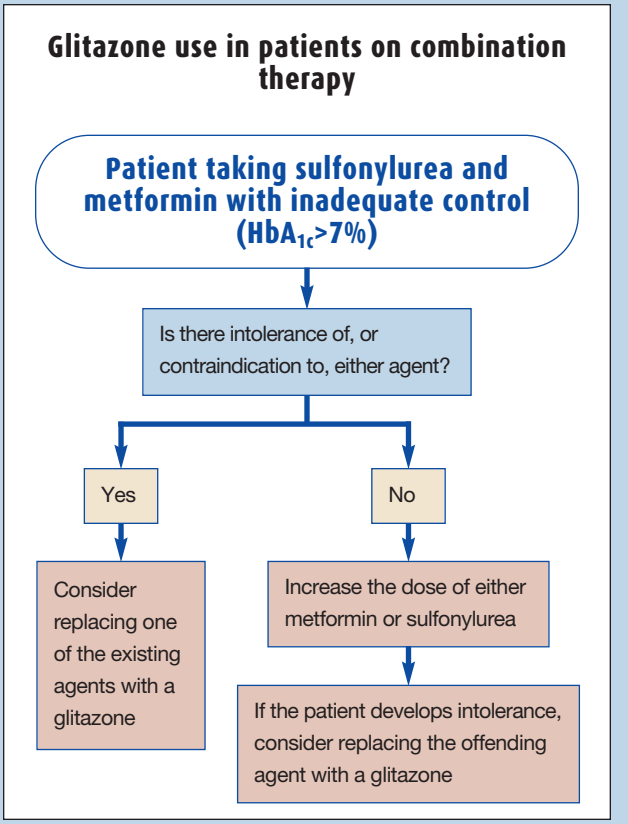

Figure B. PBS authority use of a glitazone in patients on combination therapy with metformin and sulfonylurea.

only in the presence of insulin resistance.[5] Thus they are of no use in patients with type 1 diabetes or the lean, insulin deficient (but insulin sensitive) patient with type 2 diabetes.[6] They should not continue to be used in patients who have not shown a response within three to six months, or in whom adverse effects are problematic. About 20% of patients will fall into the category of nonresponders.

How are they used?

The usual starting dose of rosiglitazone is 4 mg, whereas that of pioglitazone is 15 or 30 mg. (There are no formal guidelines on which of the pioglitazone doses to use.) Both medications can be taken at any time of the day, before, with or after food.

Although the glitazones are rapidly absorbed and reach peak levels within a few hours, because their mode of action involves genetic transcription of proteins, their glucose-lowering effect does not occur immediately. There is an unpredictable delay in their onset of action (at least one week, but usually about two to four weeks) and the time for their maximal effect to occur (up to three months or more). Thus increasing the dose of either agent is considered after two to three months and usually done if there has been a modest response, or if there has been a good response and it is felt that greater improvements could be obtained. It is important to note that, unlike conventional antidiabetic medications, they may take six to eight weeks to have any effect in some people. Rosiglitazone can be taken twice daily (4 mg twice daily), but there seems to be no reason to use this regimen in preference to 8 mg once daily, if that dose is being used.

Biochemical monitoring

The glitazones do not increase serum insulin levels, and are very unlikely to cause hypoglycaemia alone or when used with metformin. However, they potentiate the glucose-lowering action of sulfonylureas and insulin. Since the glitazones typically take weeks to months to achieve significant and peak effects, patients who are using sulfonylureas or insulin must monitor their capillary blood glucose levels carefully when starting glitazone therapy.

Since the now-withdrawn troglitazone has been linked with serious hepatotoxicity, it is suggested that alanine aminotranferase (ALT) levels be measured second-monthly for the first year and periodically thereafter when the newer glitazones are used.

Potential drug interactions

The metabolism of rosiglitazone and pioglitazone involves cytochrome P450 isoforms; however, so far, no clinically significant drug interactions have been

Case study 1. Use of pioglitazone with metformin

Mrs Jones, a 75-year-old pensioner who lives alone, has type 2 diabetes, which was diagnosed eight years ago. She has mobility problems due to osteoarthritis, known osteoporosis with fracture after a fall, and a BMI of 27 kg/m^2. Initially, she was treated with diet and exercise therapy; she started taking metformin four years ago. Her HbA_{1c} was 8.4% at the start of therapy. It decreased to 7.2% but began increasing 18 months ago despite increasing the metformin dose to 1 g twice daily. Her latest HbA_{1c} was 8.6%. Gliclazide 40 mg twice daily was added to the regimen.

Four days ago, Mrs Jones had a hypoglycaemic episode resulting in a near fall.

Discussion

Because it is essential that Mrs Jones minimises the risk of hypoglycaemia, the occurrence of a 'hypo' shortly after starting a sulfonylurea suggests that she will not tolerate such therapy; it could also be stated that sulfonylureas in this case are contraindicated.

Case continued

Gliclazide was slowly withdrawn and pioglitazone 15 mg daily was added to the regimen. At the follow up visit with her endocrinologist three months later, the patient's HbA_{1c} was 7.2% and her fasting and postprandial blood sugar levels were continuing to improve.* Her weight had increased by 1.5 kg but no other adverse effects were reported. The regimen was therefore continued.

* Improvements in glycaemic control would be expected to occur before three months; this time period is indicated because HbA_{1c} tests are appropriately ordered at these intervals.

Case study 2. Use of rosiglitazone with a sulfonylurea

Mr Collins, a 75-year-old retired accountant, has a BMI of 29 kg/m^2. Type 2 diabetes was diagnosed six years ago when his routine fasting blood sugar level was 12.7 mmol/L. Other laboratory tests revealed moderate proteinuria, serum creatinine 280 µmol/L, and creatinine clearance (calculated)* 28 mL/min.

He was started on glibenclamide on diagnosis. At the start of therapy, his HbA_{1c} was 8.7%. It decreased to 7.6% on therapy, but rose slowly over time despite increasing the glibenclamide dose to 15 mg daily. His latest HbA_{1c} was 8.8%. He is now on antihypertensive therapy (ACE inhibitor).

Discussion

Proteinuria and a creatinine clearance less than 30 mL/min suggest moderate renal impairment (consistent with diabetic nephropathy). Renal impairment means that metformin therapy is contraindicated due to an increased risk of lactic acidosis.

Case continued

Rosiglitazone 4 mg daily was added to the regimen. At his three-month review with his endocrinologist, Mr Collins's HbA_{1c} was 7.8% and his home blood sugar levels had improved somewhat but stabilised.† His weight had not changed and no side effects were noted.

The rosiglitazone dose was increased to 8 mg daily. Three months later his HbA_{1c} was 7.2% and home blood sugar levels were still decreasing gradually.† The regimen was continued.

* Creatinine clearance (CrCl) using the Cockroft-Gault equation: CrCl (ml/min) equals (140 minus age) times weight (kg) times 1.2 divided by serum creatinine (µmol/L). † Note that improvements in glycaemic control would be expected to occur before three months; this time period is indicated because HbA_{1c} tests are appropriately ordered at these intervals.

seen. Caution should be exercised when using glitazones in combination with other drugs metabolised by these enzymes. Since neither drug exhibits significant renal excretion, they can be used in patients with significant renal impairment (although caution should be used in those predisposed to fluid retention).

Adverse effects and contraindications

Weight gain

The main adverse effect of the glitazones is weight gain, which occurs in most, but not all, patients. However, central (intra-abdominal, or visceral) fat, which is more metabolically harmful than peripheral fat, is not increased and may decrease with glitazone therapy.[4] The degree to which the glitazones cause weight gain varies. It is also dose-dependent. Patients may be advised that weight gain in the order of 2 to 3 kg may occur, with most of this increase seen in the first six months or so. Thereafter, body weight may reach a plateau. It is known that the increase in fat mass may be augmented when glitazones are used in combination with sulfonylureas and insulin (particularly the latter) and minimised when used with metformin. Patients who adhere strictly to lifestyle advice are generally likely to gain less weight than others.

Fluid retention and cardiac failure

An important class effect is fluid retention, causing peripheral oedema in 3 to 5% of patients. The rate is significantly higher in patients taking concomitant insulin therapy. The oedema is generally mild and similar to that seen with the nondihydropyridine calcium channel blockers. Unless it causes discomfort, it does not usually require treatment, but compression stockings may be useful, and occasionally judicious use of loop diuretics may be appropriate. The increased plasma volume sometimes causes a small decrease in haemoglobin levels due to haemodilution, but this is rarely clinically significant.

Table 2. Heart failure: NYHA classification*

Class I
Symptoms (e.g. dyspnoea) with more than ordinary activity

Class II
Symptoms with ordinary activity

Class III
Symptoms with minimal activity

Class IV
Symptoms at rest

* New York Heart Association classification.

Unfortunately, fluid retention in patients with subnormal cardiac reserve may precipitate overt cardiac failure. Roughly 1% of patients treated with rosiglitazone or pioglitazone (or, indeed insulin) develop congestive heart failure, and this increases to 2 to 3% when glitazones are combined with insulin. Congestive heart failure is more likely with higher doses of these medications and in patients at risk of heart failure. Thus glitazones are contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure (see Table 2) and should be used with caution in anyone with lesser degrees of, or at risk of, heart failure.

If there is any concern about a patient's cardiac status, specialist referral is indicated before using glitazones. If patients develop significant weight gain or oedema after starting glitazone therapy, they should consult their GP or specialist without delay.

Patients with abnormal liver function tests

Although the relation between troglitazone and hepatotoxicity is likely to be peculiar to that particular drug, caution dictates that the whole glitazone class ought not be used in patients with ALT levels greater than 2.5 times the upper limit of normal.

Other contraindications

Because of the absence of safety data, the glitazones should not be taken by women who are pregnant, breastfeeding or lactating, or by patients under the age of 18 years.

Shared care

The entry of the glitazones into current diabetes management provides a good opportunity for shared care between endocrinologists and GPs, whereby patients are in regular contact with both. As the clinical cases on page 62 illustrate, the management of patients with glitazones can be complicated, and specialist consultation is recommended especially since these medications were prescribed mainly by specialists until late last year.

Conclusions

The glitazones represent a new and unique mode of therapy for patients with type 2 diabetes. Their action primarily produces redistribution of fatty acids to peripheral fat. This results in reduced fatty acid concentrations in the circulation, liver and muscle and improves insulin sensitivity. The potential benefits of the glitazones extend beyond glucose lowering and include attenuation of the adverse metabolic effects of insulin resistance. MT

References

1.UK Prospective Diabetes Study (UKPDS) Group. Effect of blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-865.

2. Larsen TM, Toubro S, Astrup A. PPARgamma agonists in the treatment of type II diabetes: is increased fatness commensurate with long-term efficacy? Int J Obesity 2003; 27: 147-161.

3. Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of the thiazolidinediones. Ann Intern Med 2001; 134: 61-71.

4. Gurnell M, Savage DB, Chatterjee VKK, O'Rahilly S. The metabolic syndrome: peroxisome proliferator-activated receptor gamma and its therapeutic modulation. J Clin Endocrinol Metab 2003; 88: 2412-2421.

5. Oakes ND, Kennedy CJ, Jenkins AB, Laybutt DR, Chisholm DJ, Kraegen EW. A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat. Diabetes 1994; 43: 1203-1210.

6. Greenfield JR, Chisholm DJ. Thiazolidinediones – mechanisms of action. Australian Prescriber 2004; 27: 67-70.

Further reading

1. Chisholm DJ, Campbell LV, Kraegen EW. Pathogenesis of the insulin resistance syndrome (syndrome X). Clin Exp Pharmacol Physiol 1997; 24: 782-784.

2. Lee C-H, Olson P, Evans RM. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. J Clin Endocrinol Metab 2003; 144: 2201-2207.

3. Furnsinn C, Waldhausl W. Thiazolidinediones: metabolic actions in vitro. Diabetologia 2002; 45: 1211-1223.

4. Mudaliar S, Henry RR. New oral therapies for type 2 diabetes mellitus: the glitazones or insulin sensitizers. Ann Rev Med 2001; 52: 239-257.

5. Bugianesi E, Zannoni C, Vanni E, Marzocchi R, Marchesini G. Non-alcoholic fatty liver and insulin resistance: a cause-effect relationship? Dig Liver Dis 2004; 36: 165-173.

6. Van Wijk JPH, de Koning EJP, Martens EP, Rabelink TJ. Thiazolidinediones and blood lipids in type 2 diabetes. Arterioscler Thromb Vasc Biol 2003; 23: 1744-1749.

7. Nesto RW, Bell D, Bonow RO, et al. AHA/ADA Consensus statement: thiazolidinedione use, fluid retention, and congestive heart failure. Circulation 2003; 108: 2941-2948.

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