First-line treatment for blood glucose control in type 2 diabetes: Are we doing enough?

Michael Kirby

Hyperglycaemia in type 2 diabetes in the past has traditionally been treated with a sulphonylurea initially; the dosage was increased until maximum levels were reached before adding metformin. In light of a recent analysis of UK prescribing data, which suggests that around 330 000 people with type 2 diabetes are on monotherapy and are missing their target of HbA_{1c} <7% (Ambery et al, 2005), it is time to re-evaluate this approach. Michael Kirby proposes that there should be a lower threshold for considering additional therapies, and discusses the options available and the evidence supporting their use.

Type 2 diabetes is a progressive disease characterised by hyperglycaemia resulting from a combination of peripheral and hepatic insulin resistance and impaired insulin secretion (Stumvoll et al, 2005). Increased levels of glucose in the blood, if prolonged, are asssociated with microvascular and macrovascular complications, including visual impairment, kidney failure, angina, myocardial infarction, stroke, foot ulceration and erectile dysfunction. Cardiovascular-related mortality is the leading cause of death in people with type 2 diabetes (Haffner et al, 1998).

The landmark UK Prospective Diabetes Study (UKPDS) has conclusively demonstrated an association between the degree of hyperglycaemia and risk of microvascular complications (Stratton et al, 2000) and shown that intensive diabetes therapy reduces the risk of long-term complications of diabetes (UKPDS Group, 1998a; UKPDS Group, 1998b). As a result, the widely accepted treatment goal for most patients with diabetes is the achievement and maintenance of glycaemic control that is as close to the normal range as possible.

Treatment of type 2 diabetes aims to achieve an HbA_{1c} level of between 6.5% and 7.5% (National Institute for Health and Clinical Excellence [NICE; formerly the National Institute for Clinical Excellence], 2003). Current treatment guidelines (NICE, 2002) recommend a 'step-up' policy, starting with advice on diet, exercise and weight loss, adding oral glucose-lowering drugs (usually a sulphonylurea or metformin), first as monotherapy, then in combination, and finally moving to insulin if blood glucose targets are not achieved.

The number of available oral glucose-lowering drugs agents has increased significantly in recent years. The availability of newer therapies, including fixed-dose combination therapies, should also lead us to re-evaluate traditional approaches to management. Clinicians are now increasingly able to target the underlying pathophysiological abnormalities responsible for type 2 diabetes.

Article points

1. The number of available oral glucose-lowering drugs agents has increased significantly in recent years.
2. Sulphonylureas, metformin, rapid-acting insulin secretagogues, α-glucosidase inhibitors, anti-obesity drugs and thiazolidinediones are all used to treat type 2 diabetes.
3. Metformin should be considered as first-line pharmacological therapy.
4. When additional therapies are required, it is important to target the underlying pathophysiological abnormalities responsible for type 2 diabetes with careful use of medications that have biological plausibility.

Key words

- Hyperglycaemia
- First-line treatment
- Thiazolidinediones

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Page points

1. Used as monotherapy, both sulphonylureas and metformin reduce HbA_{1c} by 1.0–1.5%, but the UK Prospective Diabetes Study (UKPDS) showed that 50% of patients will require additional therapies to achieve glycaemic targets 3 years after diagnosis.
2. The UKPDS also showed that sulphonylurea therapy reduces microvascular but not macrovascular complications, whereas metformin reduces both all-cause mortality and diabetes-related end points when used as monotherapy in obese patients with type 2 diabetes.
3. Furthermore, early addition of metformin in patients with suboptimal control while on maximal sulphonylurea therapy improves glycaemic control.
4. However, there is growing concern that sulphonylureas may contribute to cardiovascular morbidity and mortality in people with diabetes.
5. This suggests that sulphonylureas should not be given to people with diabetes who have pre-existing coronary disease.

Current drug treatments for type 2 diabetes

Sulphonylureas and metformin

Sulphonylureas have been a cornerstone of drug therapy for type 2 diabetes for more than 25 years. These drugs stimulate the secretion of insulin from pancreatic β-cells. However, excessive insulin levels may lead to hypoglycaemia (occasionally severe; Ferner and Neal, 1998) and weight gain. The weight gain is typically around 2–5 kg (UKPDS Group 1998b), which may be discouraging in patients who are already prone to obesity and are frequently struggling to lose weight.

Metformin is the preferred treatment option for patients who are overweight or obese (NICE, 2002). Metformin lowers blood glucose by inhibiting hepatic glucose production, although it may also increase glucose uptake by skeletal muscle. Because it has no direct effect on the pancreatic β-cells and therefore no effect on insulin secretion, metformin does not cause weight gain or hypoglycaemia. Side effects are mainly gastrointestinal and minor (abdominal discomfort, diarrhoea and bloating; Bailey and Feher, 2004).

Used as monotherapy, both sulphonylureas and metformin reduce HbA_{1c} by 1.0–1.5% (Cheng and Fantus, 2005). However, the UKPDS showed that around 50% of patients treated with a single antidiabetic agent will require additional therapies to achieve glycaemic targets 3 years after diagnosis (Turner et al, 1999).

The UKPDS also showed that treatment with sulphonylureas reduced microvascular complications but had no effect on macrovascular complications (UKPDS Group, 1998b). In contrast, metformin reduced both all-cause mortality and diabetes-related end points when used as monotherapy in obese patients with type 2 diabetes (UKPDS Group, 1998a). Furthermore, early addition of metformin in patients with suboptimal control while on maximal sulphonylurea therapy improved glycaemic control (UKPDS Group, 1998c).

However, there is growing concern that the use of sulphonylureas may contribute to cardiovascular morbidity and mortality in people with diabetes. Analysis of clinical practice records suggests that sulphonylurea monotherapy may be associated with increased all-cause and cardiovascular mortality compared with metformin therapy, alone or in combination with sulphonylurea (Johnson et al, 2002). Concerns have arisen (Simpson et al, 2006), given the potential of sulphonylureas to act on potassium channels and block ischaemic preconditioning and also to impede early responses to ischaemia, such as coronary artery vasodilatation and recruitment of coronary collaterals. This suggests that sulphonylureas should not be given to people with diabetes who have pre-existing coronary disease (Connaughton and Webber, 1998).

Rapid-acting insulin secretagogues

Rapid-acting insulin secretagogues, such as nateglinide and repaglinide, also stimulate insulin secretion. They can be useful for reducing postprandial hyperglycaemia and allow for more flexibility in lifestyle if meals have to be skipped (Standl and Fuchtenbusch, 2003).

α-Glucosidase inhibitors

Acarbose is the only currently available member of this class of antidiabetic agents. It acts by delaying carbohydrate absorption, thereby attenuating postprandial peak glucose levels. However, acarbose is associated with diarrhoea, flatulence and bloating and requires slow dose titration (Ahmann and Riddle, 2002). Thus it should only be used in patients who are unable to tolerate other oral treatments (Department of Health, 2006).

Anti-obesity drugs

In overweight individuals with type 2 diabetes, the use of the anti-obesity drug orlistat (Xenical; Roche) may be a useful aid to weight loss (in conjuction with diet and exercise) and may thereby help to reduce the onset of diabetes. Orlistat exerts its effects by inhibiting lipase enzymes in the stomach and intestine. Dietary fats are thus not broken down into a form that can be absorbed and the resultant reduction in fat absorption leads to weight loss (NICE, 2002).

Thiazolidinediones

The thiazolidinediones (TZDs) are the most recent addition to the antidiabetic armamentarium. These drugs function as

agonists of the peroxisome proliferator-activated receptor gamma (PPARγ), located mainly in adipose tissue. As well as lowering blood glucose, these drugs also enhance vascular function, ameliorating the dyslipidaemia and inflammatory effects of type 2 diabetes. They increase muscle insulin sensitivity and may also have positive effects on pancreatic β-cell function (Stumvoll et al, 2005).

In addition, there is growing evidence to suggest that TZDs may have multiple positive effects on cardiac function, including diminished vascular resistance, improved cardiac metabolism, positive inotropic effects, coronary vasodilation, increased natriuretic peptide production, improved endothelial function, and attenuation of cytokines (Shiomi et al, 2002; Wang et al, 2003). Furthermore, TZDs may reduce the risk of developing atherosclerotic disease by beneficially affecting blood pressure, carotid intimal thickening (Koshiyama et al, 2001), migration of vascular smooth muscle cells, and other indirect markers of atherosclerosis and vessel health (Haffner et al, 2002).

The two currently available TZDs, rosiglitazone and pioglitazone, are approved for the treatment of type 2 diabetes. They are licensed for monotherapy if metformin is contraindicated or not tolerated, where they lower HbA_{1c} to a similar extent to sulphonylureas and metformin (Cheng and Fantus, 2005). However, their major use is in combination therapy in patients whose glycaemia is insufficiently controlled by metformin or sulphonylurea monotherapy. Guidance issued by NICE recommends that people with type 2 diabetes who are unable to take metformin and sulphonylurea combination therapy because of intolerance or a contraindication to one of the drugs may be offered combination treatment with a TZD as an alternative to insulin (NICE, 2003).

Page points

1. Evidence suggests that thiazolidinediones (TZDs) may have multiple positive effects on cardiac function and may reduce the risk of developing atherosclerotic disease.
2. TZDs are licensed for monotherapy if metformin is contraindicated or not tolerated, but their major use is in combination therapy in patients whose glycaemia is insufficiently controlled by metformin or sulphonylurea monotherapy.

Page points

1. Modelling of the relationship between thiazolidinedione treatment and HbA_{1c} over extended periods suggests that in overweight and obese people with type 2 diabetes the combination of rosiglitazone and metformin is a cost-effective option compared with the combination of metformin and sulphonylurea.
2. Rosiglitazone combination therapy was predicted to lengthen life expectancy and improve quality of life: 131 and 209 additional quality-adjusted life years per 1000 patients in the obese and overweight cohorts respectively.
3. The recently published PROactive study results add more weight to the evidence.
4. The study's primary end point showed no statistically significant inter-group differences.
5. However, a secondary outcome was that, over a 3-year period, pioglitazone prevented 21 myocardial infarctions, strokes or deaths for every 1000 patients treated.

The case for thiazolidinediones

Rosiglitazone is effective as monotherapy in patients who are inadequately controlled by lifestyle interventions (Lebovitz et al, 2001). In addition, combination treatment with metformin and rosiglitazone has been shown to improve glycaemic control, insulin sensitivity and β-cell function more effectively than treatment with metformin alone in people with type 2 diabetes (Fonseca et al, 2000; Nadra et al, 2004). Data from open-label studies confirm these findings and also provide evidence of sustained glycaemic control for at least 2.5 years with combination therapy (Jariwala et al, 2003).

Studies have demonstrated a beneficial effect of the TZDs on surrogate markers of atherosclerosis: pioglitazone, in particular, has been shown to have a positive effect on lipids, notably decreasing triglyceride levels (Cheng and Fantus, 2005). However, it is important to look beyond lipid management. Recent data indicate that rosiglitazone may protect the vascular wall by improving the features of metabolic disorders and by reducing pro-inflammatory responses and the occurrence of coronary events in patients with diabetes and coronary artery disease after percutaneous coronary intervention (Wang et al, 2005).

The major side effect of the TZDs is weight gain (Vasudevan and Balasubramanyam, 2004), which seems to be linked to the effect of the drugs on adipose cell differentiation and triglyceride storage. Weight gain is of a similar magnitude to that seen with sulphonylureas but appears to be distributed peripherally rather than viscerally, and so is less metabolically harmful. Other side effects include fluid retention leading to peripheral oedema and a mild haemodilution following sodium and water retention, resulting in anaemia in some patients (Nesto et al, 2003). Less frequently, there is a risk of congestive heart failure, which necessitates careful patient selection (Nesto et al, 2003).

A recent observational study of more than 16000 older people with diabetes discharged after hospitalisation with the principal discharge diagnosis of heart failure suggests that 1-year mortality rates were lower in those treated with TZDs and metformin compared with those treated with neither drug, although there was a higher risk of readmission among those treated with a TZD (Masoudi et al, 2005).

The ability of the TZDs to reduce cardiovascular risk is being assessed in several large outcome studies. However, modelling of the relationship between treatment and HbA_{1c} over extended periods (derived from the UKPDS) suggests that the combination of rosiglitazone with metformin is a cost-effective option compared with the combination of metformin and sulphonylurea in overweight and obese people with type 2 diabetes (Bagust et al, 2003; Beale et al, 2003). Patients treated with rosiglitazone combination therapy were predicted to have a longer life expectancy, gaining 123 and 140 additional life-years per 1000 patients in the obese and overweight cohorts, respectively, while improvements in morbidity and a delay in the start of insulin therapy result in a projected improvement in quality of life. These effects combined yield 131 and 209 additional quality-adjusted life years per 1000 patients in the obese and overweight cohorts, respectively.

The long-awaited publication of the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive; Dormandy et al, 2005) has added more weight to the evidence. The 5000-patient, prospective, randomised trial investigated whether the addition of pioglitazone could reduce macrovascualr morbidity and mortality in people with type 2 diabetes who had already suffered a cardiovascular event. The key findings of the study were that adding pioglitazone to existing therapy in these high-risk patients:

- produced no statistically significant difference between the intervention and placebo groups in the primary composite end point (19.7 versus 21.7% had at least one primary event, respectively)
- led to a significant reduction in the number of deaths, heart attacks and strokes (16% reduction in this main secondary composite end point versus placebo; $P<0.027$)
- resulted in significantly better glycaemic control (absolute HbA_{1c} change from baseline, -0.8 versus -0.3%; $P<0.0001$)
- significantly reduced dyslipidaemia (change in high-density-to-low-density lipoprotein-

Table 1. Therapeutic indications for currently licensed thiazolidinediones.

Rosiglitazone	Indicated in the treatment of type 2 diabetes mellitus as the following. ● *Oral monotherapy:* – in patients (particularly overweight patients) who are inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance. ● *Dual oral therapy:* – in combination with metformin in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin – in combination with sulphonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite monotherapy with a sulphonylurea. ● *Triple oral therapy:* – in combination with metformin and a sulphonylurea in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.
Pioglitazone	Indicated in the treatment of type 2 diabetes mellitus as the following. ● *Oral monotherapy:* – in patients (particularly overweight patients) who are inadequately controlled by diet and exercise, for whom metformin is inappropriate because of contraindications or intolerance. ● *Oral combination treatment (in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea):* – in combination with metformin (particularly in overweight patients) – in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.

Source: www.emc.medicines.org.uk (accessed 01.03.2006)

Page points

1. A recent position statement by the Association of British Clinical Diabetologists concluded that the addition of a thiazolidinedione (TZD) to metformin is the preferred second-line oral antidiabetic therapy in obese patients as they are frequently insulin resistant.
2. It also suggests that there is a place for 'triple therapy' of metformin, a sulphonylurea and TZD in very obese patients and in those unwilling to consider insulin therapy, which is supported by clinical trial evidence.

cholesterol ratio, -9.5 versus -4.2%; $P<0.0001$; and change in triglycerides, -11.4 versus -1.8%; $P<0.0001$)

- significantly delayed the progression to insulin (53% reduced risk of permanent insulin use versus placebo; $P<0.0001$).

It should be noted that the study's primary end point (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, or amputation above the ankle) showed no statistically significant inter-group differences. This was mainly due to an increased number of leg revascularisations in the pioglitazone group, compared with the placebo group.

Patients with known heart failure were excluded from the trial, and at entry to the study mean body mass index was 31 kg/m^2, mean blood pressure was 143/83 mmHg, 14% of participants were smokers, 43% were on a statin and 62% were on metformin.

The study indicated an increased rate of oedema and heart failure in the pioglitazone group, but mortality due to heart failure did not differ between the groups. The investigators concluded that the increased reporting of heart failure in the pioglitazone group might, at least in part, indicate a diagnostic bias because of the increased oedema in the pioglitazone group. They also noted that heart failure was not a centrally adjudicated event. There were some acknowledged weaknesses in the study design regarding the choice of primary end point.

All in all, however, over a 3-year period pioglitazone prevented 21 myocardial infarctions, strokes or deaths for every 1000 patients treated. This equates to one major cardiovascular event avoided for every 48 patients treated. This was a secondary outcome and the study was powered for analysis of the primary end point – we therefore await further evidence from future trials of this group of drugs to corroborate this result.

A recent position statement by the Association of British Clinical Diabetologists (ABCD; Higgs and Krentz, 2004) concluded that the addition of a TZD to metformin is the preferred second-line oral antidiabetic therapy in obese patients as they are frequently insulin resistant. The statement noted that TZDs may confer additional benefits in cardiovascular risk factors (lipids, blood pressure and microalbuminuria) and that clinical trials were in progress to determine whether this translates into meaningful reduction in cardiovascular disease.

It also suggests that there is a place for 'triple therapy' of metformin, a sulphonylurea and TZD in very obese patients and in those unwilling to consider insulin therapy, which is supported by clinical trial evidence (Kiayias et al, 2002). Therapeutic indications for the currently licensed TZDs are shown in *Table 1*.

However, the ABCD statement stresses that TZDs should not be considered a substitute for insulin in patients with poor glycaemic control on the maximum tolerated dose of sulphonylurea and metformin. Furthermore, because of the risk of oedema and heart failure, use of a TZD with insulin is not recommended.

Page points

1. Metformin should be considered first-line pharmacological therapy.
2. When additional therapies are required, it is important to target the underlying pathophysiological abnormalities responsible for type 2 diabetes with careful use of medications that have biological plausibility.
3. In the author's view, the most logical approach is to combine metformin with a thiazolidinedione (TZD) rather than a sulphonylurea.
4. By reducing insulin resistance, improving glycaemic control, and preserving β-cell function with a TZD early in the course of therapy, it is possible that durable glycaemic control will be achieved and both microvascular and macrovascular complications will be reduced.

If this approach is advised by a clinician, it is essential to screen for oedema, heart failure and significant left ventricular dysfunction and to ensure that the patient understands and accepts the increased risks (Higgs and Krentz, 2004).

Conclusion

The aim of management for patients with type 2 diabetes is to control blood glucose levels and thereby reduce microvascular and macrovascular complications. Therapy was traditionally initiated with a sulphonylurea; the dosage was increased until maximum levels are reached before adding metformin. This approach needs to be re-evaluated: recent analysis of UK prescribing data suggests that around 330 000 people with type 2 diabetes are on monotherapy and are missing their glycaemic control target of HbA_{1c} <7% (Ambery et al, 2005).

In the author's opinion, there should ideally be a lower threshold for considering additional therapy options, preferably with a greater focus on earlier use of additional therapies with complementary effects. However, this has implications for patient compliance, which is inversely related to the prescribed number of doses a patient is required to take per day. Studies have shown that simpler, less frequent dosing regimens result in better compliance (Claxton et al, 2001). Fixed-dose combination products clearly offer the potential for enhanced treatment adherence and improved target achievement.

The British Hypertension Society has produced a four-step algorithm, incorporating all classes of antihypertensive drugs, to improve blood pressure control. It recommends drug combinations and sequences similar to those used in clinical trials, and in the discussion supports the use of fixed combinations where appropriate (Williams et al, 2004). Further evidence of the benefit of fixed combinations comes from a retrospective study of adherence to a fixed-dose combination of rosiglitazone and metformin, which showed significant improvement in adherence (Vanderpoel et al, 2004).

Most people with type 2 diabetes are overweight or obese, and most have insulin resistance. It is therefore essential that we continue to focus on diet and exercise programmes. Metformin should be considered as first-line pharmacological therapy (NICE, 2002). When additional therapies are required, it is important to target the underlying pathophysiological abnormalities responsible for type 2 diabetes with careful use of medications that have biological plausibility.

In the author's view, the most logical approach is to combine metformin with a TZD rather than a sulphonylurea. By reducing insulin resistance, improving glycaemic control, and preserving β-cell function with a TZD early in the course of therapy, it is possible that durable glycaemic control will be achieved and both microvascular and macrovascular complications will be reduced. Furthermore, early use of an insulin-sensitising agent, either alone or in combination, could plausibly improve both acute and long-term outcomes in people with type 2 diabetes.

The clinical trial evidence for prevention of cardiovascular disease in diabetes is largely based on single risk factor interventions. However, the Steno-2 study has provided good evidence for the cardiovascular benefits following a multifactorial intervention programme (Gaede et al, 2003; Malmberg et al, 2005). This article has focused on glycaemia, but clearly careful management of hypertension and hyperlipidaemia combined with weight loss and an exercise programme are equally crucial in the management of people with type 2 diabetes. ■

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