Happy anniversary, metformin!

Roger Gadsby

Article points

1. In 1957 metformin was introduced as an agent to lower blood glucose levels in people with type 2 diabetes.
2. Metformin lowers glycaemia as effectively as any other oral medication, plus it is the only oral agent that reduces adverse cardiovascular outcomes.
3. NICE recommends metformin as first-line monotherapy in overweight individuals with type 2 diabetes.
4. Side effects can be minimised by starting with a low dose of 500 mg daily for 2 weeks before titrating up to 500 mg twice daily over 2–4 weeks.
5. Prolonged-release metformin is associated with fewer gastrointestinal side effects than generic standard-release metformin.

Key words

- Metformin
- Sustained release
- Guidelines
- Adverse events

Dr Roger Gadsby is a GP in Nuneaton, Associate Clinical Professor at the Warwick Medical School, University of Warwick, and Medical Advisor at Warwick Diabetes Care.

2007 is the 50th Anniversary of the launch of metformin in Europe (Campbell et al, 1996). This article reviews its progress from humble beginnings to its place today as the initial monotherapy of choice for the oral treatment of type 2 diabetes.

In Medieval times the plant *Galega officinalis* (commonly called Goat's rue, French lilac or Italian fitch; shown on cover) was found to relieve the prolific urination that can accompany diabetes. Later the active ingredient was found to be galegine, also known as isoamylene guanidine (Witters, 2001). In 1918 it was shown that an infusion of guanidine produced a lowering of blood glucose (Watanabe, 1918). While guanidine itself was too toxic to be used as a therapy, substances containing two linked guanidine rings, the biguanides, were found to lower blood glucose levels and be less toxic than the single-ring form (Witters, 2001).

In 1957 bimethylbiguanide (metformin) was introduced as an agent to lower blood glucose levels in people with type 2 diabetes (Campbell et al, 1996). Two other biguanides, phenformin and buformin, also available in the 1950s, were withdrawn from the market worldwide in the late 1970s owing to an elevated risk of lactic acidosis (Bailey and Turner, 1996).

Overall, metformin was found to be a much safer drug and thus became widely used in Europe, usually as an add-on therapy to a sulphonylurea. However, it received its license in the US in 1995 (Bailey and Turner, 1996). Preparation for this launch necessitated another round of research into the safety and effectiveness of metformin, the favourable results of which supported FDA approval. Within a few years it became the most widely prescribed glucose-lowering agent in the USA (Hundal and Inzucchi, 2003).

Metformin therapy improves insulin sensitivity, as shown by a reduction in fasting plasma glucose and insulin concentrations, and is not effective in the absence of insulin (Bailey and Turner, 1996). In people with type 2 diabetes the glucose-lowering effect is attributed mainly to decreased hepatic glucose output and enhanced peripheral glucose uptake. Several other actions may contribute, such as increased intestinal use of glucose and decreased fatty acid oxidation (Bailey and Turner, 1996).

Metformin in diabetes guidelines today

In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines on glycaemic control in type 2 diabetes recommend metformin as the initial monotherapy of choice in all people who are overweight (BMI >25 kg/m^2). The document also advises that metformin should be considered as the initial monotherapy for type 2 diabetes in those with a BMI below 25 kg/m^2 (NICE, 2002).

The International Diabetes Federation (IDF) recommend metformin monotherapy unless there is evidence of renal impairment (IDF, 2005). NICE state that metformin should not be prescribed if serum creatinine levels are greater than 130 µm/l and should be stopped if they rise above 150 µm/l (NICE, 2002). Now

that serum creatinine levels are being translated into estimated glomerular filtration rates (eGFR) the equivalent eGFR figures are likely to be 30 and 45 ml/min, respectively.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) joint guidelines on hyperglycaemia in type 2 diabetes recommend, in the absence of specific contraindications, that metformin be introduced along with lifestyle interventions immediately after diagnosis of type 2 diabetes (Nathan et al, 2006). Metformin is recommended as the intitial pharmacological therapy owing to: its ability to lower HbA_{1c} by approximately 1.5%; the absence of associated weight gain or hypoglycaemia; low levels of side effects; high levels of patient acceptance; and relatively low cost (Nathan et al, 2006).

Further evidence comes from the UK Prospective Diabetes Study (UKPDS), in which a group of obese people newly diagnosed with type 2 diabetes were randomised to either receive metformin monotherapy or manage their diabetes through diet alone. Compared with the group treated by conventional means, the metformin group had a 32% risk reduction for diabetes-related end points (including myocardial infarction and stroke; P=0.002) and a 42% reduction in risk for diabetes-related deaths (UKPDS, 1998).

Metformin improves glycaemia as effectively as other oral medication and on the evidence of the UKPDS it reduces cardiovascular outcomes (DeFronzo and Goodman, 1993; UKPDS, 1998). The precise mechanism by which metformin achieves this reduction of adverse cardiovascular outcomes remains to be clarified.

In the Diabetes Prevention Study several thousand people with impaired glucose tolerance (IGT) were divided into three groups (Diabetes Prevention Programme Research Group, 2002). One group received a diet and exercise programme that was aimed at achieving a weight reduction of 7% and moderate physical activity, for example, brisk walking for 150 minutes per week. People in the active arm of the study had regular one-to-one sessions with their case manager in the first 24 weeks and then monthly sessions for the remaining period of the study. Fifty per cent of people in this group achieved the weight reduction target at 24 weeks and 74% achieved the exercise target. A control group received 'general advice' and another group received general advice plus metformin therapy. Those in the lifestyle plus exercise group reduced their risk of developing diabetes by 58% and those in the metformin group reduced their risk of developing diabetes by 31%, both compared with the control group. Metformin is therefore now being used off license by some prescribers in selected individuals with IGT who are unable to adhere to lifestyle change.

Additionally, metformin has been recommended as an adjunct to other regimens, the details of which are shown in *Table 1*.

Adverse events

Metformin can cause gastrointestinal side effects such as abdominal pain, nausea, diarrhoea and a metallic taste in the mouth. Approximately 10–20% of those prescribed it do not continue due to these side effects (DeFronzo and Goodman, 1993). However, side effects can be minimised by starting with a low dose of 500 mg daily for 2 weeks before titrating up to 500 mg twice daily over 2–4 weeks.

In the author's clinical practice, if 500 mg BD of metformin does not produce adequate glycaemic control, the dose is uptitrated to 1 gm BD. Furthermore, clinical experience suggests that gastrointestinal side effects are often dose dependent, therefore it could be advised to not prescribe more than 2 g of metformin daily.

Page points

1. Metformin is recommended as the initial pharmacological therapy owing to its ability to lower glycaemia by approximately 1.5%; the absence of associated weight gain or hypoglycaemia; low levels of side effects; high level of acceptance; and relatively low cost.
2. Approximately 10–20% of those prescribed metformin do not continue owing to these side effects.

Table 1. Metformin in combination with other glucose-lowering therapies.

- Can be used with sulphonylureas or glitazones as dual therapy.
- Can be used as part of a triple oral agent regime – with a sulphonylurea and a glitazone.
- Very helpful when insulin treatment needs to be initiated in someone with type 2 diabetes. By increasing the sensitivity of body tissues to insulin, metformin provides a highly synergistic action. The advantages of continuing metformin when introducing insulin include the following.
  - A decrease in the weight gain associated with insulin therapy.
  - A greater reduction in HbA_{1c} than with insulin alone.
  - Lower insulin dose requirements.

Page points

1. Lactic acidosis is a very rare but serious adverse effect in metformin-treated individuals with an estimated incidence of 0.01–0.08 cases per 1000 patient years.
2. When metformin is used as labelled the increased risk of lactic acidosis is either zero or so close to zero that it cannot be factored into ordinary clinical decision making.
3. Prolonged-release metformin is associated with fewer gastrointestinal side effects than generic metformin.
4. Some individuals who cannot tolerate more than 500 mg BD of generic immediate-release metformin will manage three or even four sustained-release metformin tablets daily.

Lactic Acidosis

Lactic acidosis is a very rare but serious adverse effect in metformin-treated individuals with an estimated incidence of 0.01–0.08 cases per 1000 patient years (Bailey and Turner, 1996). Predominantly, lactic acidosis occurs because one or more contraindication was overlooked, leading to high plasma concentrations of metformin. In practice, where this agent is used widely, lactic acidosis is not regarded as a major problem, probably owing to adherence to the exclusion criteria (Bailey and Turner, 1996).

Metformin is associated with lactic acidosis in individuals with conditions that themselves cause lactic acidosis, such as heart failure, hypoxia or sepsis, but it is impossible to determine to what extent, if at all, metformin contributes to the development of lactic acidosis in any individual case. When metformin is used as labelled the increased risk of lactic acidosis is either zero or so close to zero that it cannot be factored into ordinary clinical decision making. If one excludes overdoses, most cases of metformin-associated lactic acidosis, particularly those resulting in fatalities, were probably not caused by metformin (Misbin, 2004).

Prolonged-release metformin

A prolonged-release metformin preparation is currently available in the UK. The 500-mg prolonged-release tablets can be given 1–4 times daily, but usually once daily. This formulation is associated with fewer gastrointestinal side effects than generic metformin (Blonde et al, 2004).

As metformin has been found to reduce adverse cardiovascular outcomes in the UKPDS, it is the author's opinion that the prolonged-release preparation be tried in all people with type 2 diabetes who are intolerant of standard metformin. This would ensure that a maximal number of individuals would receive the benefits of metformin and could prove more cost effective than having to switch to more expensive treatments.

In the author's clinical experience, a number of the individuals who suffered unacceptable gastrointestinal adverse events from small doses of metformin can tolerate two prolonged-release standard metformin tablets daily. Some individuals who cannot tolerate more than 500 mg BD of standard metformin will manage three or even four prolonged-release metformin tablets daily.

Conclusion

Metformin prescribing has risen significantly in the UK over the past 9 years. During this time, there has been little pharmaceutical industry promotion as most of the prescribing has been of the formulation. The rise in prescribing may therefore be evidence that diabetes healthcare professionals are practising evidenced-based medicine. ■

Bailey CJ, Turner RC (1996) Metformin. *New England Journal of Medicine* **1334**: 574–9

Blonde L, Dalley GE, Jabbour SA et al (2004) Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. *Current Medical Research and Opinion* **20**: 565–72

Campbell RK, White JR, Saulie BA (1996) Metformin: a new oral biguanide. *Clinical Therapeutics* **18**: 360–71

DeFronzo RA, Goodman AM (1993) Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *New England Journal of Medicine* **333**: 541–9

Diabetes Prevention Programme Research Group (2002) Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *New England Journal of Medicine* **346**: 393–403

Hundal RS, Inzucchi SE (2003) Metformin: new understandings, new uses. *Drugs* **63**: 1879–94

International Diabetes Federation (2005) *Global Guideline for Type 2 Diabetes 2005*. IDF, Brussels

Misbin RI (2004) The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care* **27**: 1791–3

Nathan DM, Buse JB, Davidson MB et al (2006) Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **29**: 1963–72

National Institute of Health and Clinical Excellence (2002) *Management of type 2 diabetes - Managing blood glucose levels (Guideline G)*. NICE, London

UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**: 854–65

Watanabe CK (1918) Studies in the metabolic changes induced by administrationof guanidine bases. I. Influence of injected guanidine hydrochloride uponblood sugar content. *Journal of Biological Chemistry* **33**: 253–65

Witters LA (2001) The blooming of the French lilac. *Journal of Clinical Investigation* **108**: 1105–7