CPD Module 1

New online learning opportunity

Hyperglycaemia in type 2 diabetes: Older blood glucose lowering therapies

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Learning objectives

After reading this article, the participant should be able to:

1. Explain the different mechanisms of action of the older oral blood glucose lowering agents.
2. Outline the indications and contraindications of each agent.
3. Evaluate the glycaemic and cardiovascular benefits of older oral blood glucose lowering agents.

Key words

- Metformin
- Sulphonylureas
- Thiazolidinediones
- Meglitinides
- Acarbose

Once type 2 diabetes is diagnosed and beyond the control of lifestyle modifications, glucose-lowering therapy must be initiated and carefully monitored using drugs that address the current understanding of the pathophysiology: impaired insulin secretion and increased insulin resistance. This article focuses on five classes of older oral antidiabetes agent: biguanides (metformin), sulphonylureas, meglitinides, alpha-glucosidase inhibitors (acarbose) and thiazolidinediones. Modes of action, indications and licences, contraindications and side effects are reviewed, along with key evidence underpinning each drug class.

Type 2 diabetes is a metabolic disorder with multiple causes, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. The development of type 2 diabetes is a gradual process. A combination of both insulin resistance (the gradual failure of peripheral tissues and the liver to respond to insulin) and reduced pancreatic beta-cell function (reduced ability of beta-cells to secrete insulin in response to hyperglycaemia) is involved, although the contribution of these two major components varies between individuals.

Type 2 diabetes is more common in older individuals, but is strongly associated with obesity and a sedentary lifestyle and is increasingly seen at a younger age (Koopman et al, 2005). Prevalence is also increased in certain ethnic groups, in particular individuals originating from South Asia, who are around three to six times more likely to develop type 2 diabetes, and to develop the condition at a younger age (Barnett et al, 2006). The latest research from Diabetes UK indicates that one person is diagnosed with diabetes every 3 minutes (Diabetes UK, 2009). Diabetes prevalence rate forecasts indicate that over

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Supported by a grant from Merck Sharp & Dohme Limited (MSD). These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. MSD had no input into the modules and are not responsible for their content.

3.6 million people (6.5% of the population) in England will have the condition by 2025 if obesity continues to rise at its current level (Yorkshire and Humber Public Health Observatory, 2008).

Over time, damage caused by high blood glucose levels affects a number of organs and leads to the long-term complications of diabetes. These can be classified broadly as microvascular complications such as retinopathy, nephropathy and neuropathy, or macrovascular complications including myocardial infarction and stroke. Both the duration of diabetes and level of blood glucose control are risk factors for the development of microvascular complications. Epidemiological extrapolation of data from the UKPDS (UK Prospective Diabetes Study) suggest that a 1 percentage point reduction in HbA_{1c} yields relative risk reductions of 14% for the incidence of myocardial infarction, and 37% for microvascular complications (Stratton et al, 2000).

Compared with the healthy population, people with diabetes have a high risk of morbidity and premature mortality from cardiovascular disease (Haffner et al, 1998; Lotufo et al, 2001; Khaw et al 2004). Myocardial infarction and stroke are the major causes of premature death in people with diabetes, and the increasing prevalence of diabetes will undoubtedly be closely followed by increases in cardiovascular morbidity and mortality.

Diabetes can be prevented or delayed through lifestyle interventions (Knowler et al, 2002; Tuomilehto et al, 2001). Lifestyle modification has the advantage that it will simultaneously help to reduce other cardiovascular risk factors such as hypertension, obesity and dyslipidaemia. Lifestyle behaviours that should be promoted for optimal management of diabetes include a healthy, balanced diet, regular physical activity, smoking cessation and sustained weight loss in the overweight (International Diabetes Federation Clinical Guidelines Task Force, 2006; National Collaborating Centre for Chronic Conditions [NCCCC], 2008). While lifestyle intervention is an integral component of diabetes management, adherence to such regimens is often difficult to achieve and maintain, and most people with type 2 diabetes will eventually require pharmacological intervention for glycaemic control.

In recent years the range of oral antidiabetes agents available has broadened. This module will summarise the role of the older, or "traditional", oral glucose-lowering agents. These include metformin (*Box 1*), sulphonylureas (*Box 2*), thiazolidinediones (TZDs, or glitazones; *Box 3*), meglitinides (*Box 4*), and alpha-glucosidase inhibitors (*Box 5*), which are differentiated from each other through a variety of mechanisms of action (*Figure 1*). The newer agents targeting the incretin system, and the various insulin preparations will be covered in subsequent modules.

Metformin

History

Metformin was first described in the scientific literature in 1957 (Ungar et al, 1957), but only received approval by the US Food and Drug Administration (FDA) for type 2 diabetes in 1994 and was first marketed in the USA in 1995. Generic formulations are now available. Metformin was an additional option to sulphonylureas or insulin in overweight people

Page points

1. Over time, damage caused by high blood glucose levels affects a number of organs and leads to the long-term complications of diabetes.
2. Compared with the healthy population, people with diabetes have a high risk of morbidity and premature mortality from cardiovascular disease.
3. Diabetes can be prevented or delayed through lifestyle interventions.
4. While lifestyle intervention is an integral component of diabetes management, adherence to such regimens is often difficult to achieve and maintain, and most people with type 2 diabetes will eventually require pharmacological intervention for glycaemic control.

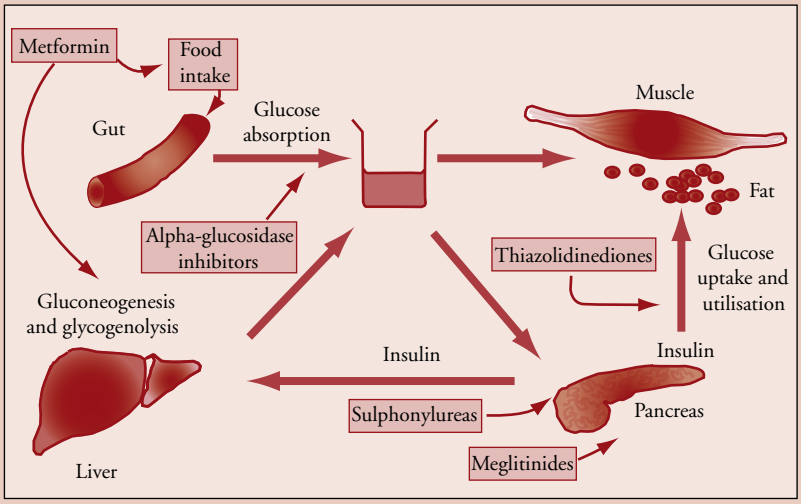

Figure 1. Sites of action of drugs used to treat type 2 diabetes (Reproduced from Greich JE and Szoke E (2006) Pathogenesis of type 2 diabetes.* In*: Skyler JS ed.* Atlas of Diabetes, Third edition. *Current Medicine Group LLC, Philadelphia, Figure 8–20 with kind permission of Current Medicine Group LLC)

CPD module

Box 1. Metformin: key facts and practical considerations.

- Low cost (£258 per patient less than conventional treatment; Clarke et al, 2001).
- Weight neutral, possibly some weight reduction as monotherapy (UKPDS Group, 1998a).
- Starting dose 500 mg once daily taken with food, slow titration up to 3 g, but the dose–response curve above 2 g is fairly flat and gastrointestinal side-effects increase (Merck Sorono, 2005).
- Review dose if eGFR is <45 mL/minute/1.73 m^2 or serum creatinine exceeds 130 µmol/l (NCCCC, 2008).
- Stop metformin if eGFR is <30 mL/min/1.73 m^2 or if serum creatinine exceeds 150 µmol/L (NCCCC, 2008).
- Slow-release formulation available.
- Fixed-dose combinations available with rosiglitazone, pioglitazone and vildagliptin.
- Reduces HbA_{1c} by approximately 1.5 percentage points (Nathan et al, 2006).
- Does not cause hypoglycaemia.

in the UKPDS (UKPDS Group, 1998a). In these people, metformin reduced the incidence of any diabetes-related endpoint by 32% compared with patients on conventional therapy (diet alone; *P*=0.0023; UKPDS Group, 1998a). Following publication of these results, metformin use increased and it is now the most widely prescribed oral antidiabetes agent in the world. Metformin is also now available in fixed-dose combinations with many other oral blood glucose lowering agents.

Mode of action

Metformin belongs to the biguanide class of antidiabetes drugs, which also included phenformin, an agent withdrawn due to a high incidence of lactic acidosis. Metformin reduces hepatic glucose production, primarily by decreasing gluconeogenesis, thereby reducing fasting plasma glucose. In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake, decreases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract (DeFronzo et al, 1991).

Indications and licence

Metformin is indicated for the treatment of type 2 diabetes, particularly in overweight people, when dietary management and exercise alone does not result in adequate glycaemic control (Merck Sorono, 2005). In all guidelines, metformin is the first-line choice of antidiabetes drug (Scottish Intercollegiate Guidelines Network, 2001; NCCCC, 2008; Nathan et al, 2009). It may be used as monotherapy or in combination with other antidiabetes agents including the sulphonylureas, TZDs, acarbose, meglitinides, dipeptidyl peptidase-4 inhibitors, exenatide or insulin.

Contraindications and side-effects

Metformin is excreted in the urine and metformin accumulation can lead to a rare risk of lactic acidosis when renal clearance is limited. As a result metformin is contraindicated in individuals with renal failure or renal dysfunction (creatinine clearance <60 mL/min; Merck Sorono, 2005). NICE recommends reviewing the dose of metformin if the serum creatinine level exceeds 130 µmol/L or the estimated glomerular filtration rate (eGFR) is below 45 mL/minute/1.73 m^2 (NCCCC, 2008). It should be used with caution in hepatic failure and alcoholism states as these conditions may also increase the risk of lactic acidosis. Other conditions that predispose to tissue hypoxaemia or reduced perfusion, such as septicaemia or myocardial infarction are also contraindications (Merck Sorono, 2005). The H_2-receptor antagonist cimetidine inhibits the renal tubular secretion of metformin, resulting in higher circulating plasma concentrations (Somogyi et al, 1987).

The most common adverse effect of metformin is gastrointestinal upset, including diarrhoea, cramps, nausea, vomiting and increased flatulence; metformin is more commonly associated with gastrointestinal side effects than most other antidiabetes drugs (Bolen et al, 2007). Gastrointestinal upset can be reduced by careful titration, or by use of a slow-release formulation (now available in 500 mg and 750 mg strengths).

It is recommended that metformin be temporarily discontinued prior to the intravascular administration of an iodinated contrast agent in radiologic studies (Merck Sorono, 2005; Thomsen and Morcos, 2003).

Page points

1. Metformin is contraindicated in individuals with renal failure or renal dysfunction.
2. The most common adverse effect of metformin is gastrointestinal upset.

Key evidence

UKPDS

Metformin was compared with insulin and sulphonylurea therapy to determine the nature of any specific advantages or disadvantages in a subset of overweight people with type 2 diabetes. Metformin was associated with a 39% risk reduction in myocardial infarction after 10 years (*P*=0.01; UKPDS Group, 1998a). Data from the 10-year, post-trial monitoring programme indicate that in the metformin group, significant risk reductions for myocardial infarction persist (33%, *P*=0.005; Holman et al, 2008).

DPP

The DPP (Diabetes Prevention Program) evaluated whether diet and exercise or metformin could prevent or delay the onset of type 2 diabetes in people with impaired glucose tolerance (IGT). Both arms were effective in reducing the progression from IGT to type 2 diabetes. Metformin was most effective in people aged 25 to 44 years old and in those with a BMI ≥35 kg/m^2 (Knowler et al, 2002).

Sulphonylureas

History

The sulphonylureas were discovered by researchers studying sulphonamide antibiotics who observed that they induced hypoglycaemia in animals (Janbon et al, 1942). The sulphonylureas are classified as first-, second-, and third-generation agents as follows:

- First generation: tolbutamide, chlorpropamide.
- Second generation: glibenclamide (glyburide in the USA and Canada), gliclazide, glipizide.
- Third generation: glimepiride.

Mode of action

The sulphonylureas are pharmacological inhibitors of potassium channels in pancreatic beta-cells and require functioning beta-cells in order to work. As a result of a direct interaction with the SUR1 receptor, the regulatory subunit of the channel, sulphonylureas stimulate insulin secretion by inducing membrane depolarisation even when there is no increase in the metabolic rate (Ashcroft and Gribble, 1999). All sulphonylureas have a similar mode of action, but differ in their affinity for SUR1. The sulphonylureas reduce both basal and postprandial glucose levels and can cause hypoglycaemia as they stimulate insulin secretion that is not glucose dependent.

Box 2. Sulphonylureas: key facts and practical considerations.

- Low cost, especially if a generic formulation is prescribed.
- Approximately 1.5 percentage point reduction in HbA_{1c} (Nathan et al, 2009).
- Effectiveness depends upon adequate beta-cell function.
- Early rapid reduction in HbA_{1c}, but the action is not sustainable (Kahn et al, 2006).
- Associated with hypoglycaemia and weight gain.
- Caution required in people with renal or hepatic impairment.
- Start with low dose and titrate slowly.
- Slow-release formulation of gliclazide available.

Indications and licence

The sulphonylureas are indicated for the treatment of type 2 diabetes and can be considered as an option for first-line glucose lowering-therapy if (NCCCC, 2008):

- The person is not overweight.
- Metformin is not tolerated or is contraindicated.
- A rapid response to therapy is required because of hyperglycaemic symptoms.

Short- and long-acting sulphonylureas are available and may be prescribed as monotherapy, or in combination with metformin, acarbose, the TZDs and the newer incretin system based therapies.

Contraindications and side-effects

In the author's experience, chlorpropamide and glibenclamide are rarely used in practice. Their long duration of action predisposes to hypoglycaemia, particularly in older people, in whom they should be avoided. Tolbutamide has a shorter duration of action, but its use in clinical practice is diminishing. The most commonly used agents are gliclazide and glipizide.

The sulphonylureas are associated with both weight gain, typically 1–4 kg in the first 6 months of therapy, and hypoglycaemia, although the risk of the latter is reduced with some of the

Page points

1. In the UKPDS, metformin was associated with a 39% risk reduction in myocardial infarction after 10 years.
2. The sulphonylureas were discovered by researchers studying sulphonamide antibiotics who observed that they induced hypoglycaemia in animals.
3. The sulphonylureas are pharmacological inhibitors of potassium channels in pancreatic beta-cells and require functioning beta-cells in order to work.
4. The sulphonylureas are indicated for the treatment of type 2 diabetes and can be considered as an option for first-line glucose lowering-therapy in certain people.

CPD module

Page points

1. The TZDs enhance the action of insulin in insulin-sensitive tissue by increasing glucose uptake in skeletal muscle and adipose tissue and decreasing hepatic glucose production.
2. An important side effect of the TZDs is fluid retention, usually manifest as peripheral oedema, which can contribute to weight gain.

newer agents.

The sulphonylureas should be used with caution in patients with hepatic or renal disease. The half-life of insulin is extended in these patients and thus there is an increased risk of hypoglycaemia.

Key evidence

UKPDS

Intensive blood glucose control with sulphonylureas or insulin, compared with conventional treatment (diet alone), was associated with a 25% reduction in microvascular complications, but no significant benefit was seen in macrovascular complications (UKPDS Group, 1998b). However, during 10 years of post-trial follow-up, a continued reduction in microvascular risk and emerging risk reductions for myocardial infarction and death from any cause were observed (this has been termed a "legacy effect"; Holman et al, 2008).

UGDP

Sulphonylurea therapy was implicated as a potential cause of increased cardiovascular disease mortality in the UGDP (University Group Diabetes Program; Klimt et al, 1970). Concerns raised by the UGDP study have not been substantiated in subsequent landmark studies including the UKPDS (UKPDS Group, 1998b) and ADOPT (A Diabetes Outcome Progression Trial; Kahn et al, 2006).

Thiazolidinediones (glitazones)

History

The first member of the TZD class, introduced in 1997, was troglitazone, but this agent was withdrawn shortly after due to reports of hepatotoxicity. Two further members of this class, rosiglitazone and pioglitazone, were introduced in 2000.

Mode of action

The TZDs work primarily by activating the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR) gamma, thereby turning on and off specific genes for the regulation of glucose, lipids and protein metabolism (Spiegelman, 1998). The effect of PPAR gamma activation is to enhance the action of insulin in insulin-sensitive tissue by increasing glucose uptake in skeletal muscle and adipose tissue and decreasing hepatic glucose production. It is also associated with a transfer of fat from visceral to subcutaneous depots.

In addition, this class of agent has been shown to reduce levels of C-reactive protein (Pfutzner et al, 2005; Goldstein et al, 2006), and, in animal studies, preserve beta-cell function (Diani et al, 2004).

Indications and licence

Pioglitazone and rosiglitazone are both indicated in the treatment of type 2 diabetes as monotherapy in people inadequately controlled by nonpharmacological measures, and in combination with metformin or sulphonylureas as dual or triple therapy (Takeda UK Ltd, 2007; GlaxoSmithKline UK, 2008). In addition, pioglitazone, but not rosiglitazone, is licensed in combination with insulin (Takeda UK Ltd, 2007). In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy (Takeda UK Ltd, 2007).

Contraindications and side-effects

An important side effect of the TZDs is fluid retention, usually manifest as peripheral oedema, which can contribute to weight gain. The likelihood of oedema increases when TZDs are used in combination with insulin and patients using this combination should be monitored carefully. In Europe, heart failure at any stage is an absolute contraindication to the use of TZDs as the oedema can be associated with new or worsened heart failure (Takeda

Box 3. Thiazolidinediones: key facts and practical considerations.

- Useful in patients with features of the metabolic syndrome.
- Cause weight gain and anaemia.
- Increased risk of fractures in post-menopausal women (Kahn et al, 2008; Spanheimer, 2007; Loke et al, 2009).
- Low risk of hypoglycaemia.
- Contraindicated in heart failure, hepatic impairment and, for rosiglitazone, acute coronary syndrome.
- Reduce HbA_{1c} by 0.5–1.5 percentage points (Nathan et al, 2009).
- Sustainability of action (Kahn et al, 2006).

UK Ltd, 2007; GlaxoSmithKline UK, 2008). The presence of an acute coronary syndrome is also a contraindication to the use of rosiglitazone (GlaxoSmithKline UK, 2008).

A decrease in the haematocrit and haemoglobin concentration usually occurs during TZD therapy, and is consistent with a dilutional anaemia.

The first available medication in the TZD class, troglitazone, was withdrawn from the market due to severe liver toxicity. Pioglitazone and rosiglitazone have not been associated with severe liver toxicity either as monotherapy or with oral antidiabetes agent or insulin combinations; however, it is recommended that liver enzymes are checked before initiating therapy in all patients and are monitored periodically thereafter based on clinical judgement (Takeda UK Ltd, 2007; GlaxoSmithKline UK, 2008).

Both TZDs are contraindicated for use in patients with hepatic impairment. Weight gain is a class effect of the TZDs either as monotherapy or in combination with other glucose-lowering agents. Most studies report an average weight gain of 1–4 kg over the first year of TZD treatment.

Long-term use of TZDs has also been associated with an increase in the risk of fractures in women, but not men, with type 2 diabetes (Loke et al, 2009).

Key evidence

ADOPT

A 4-year trial investigating the durability of the anti-hyperglycaemic effects of rosiglitazone, metformin and glibenclamide in drug-naive patients found that initial treatment with rosiglitazone slowed the progression to monotherapy failure more effectively than either metformin or glibenclamide, albeit with weight gain (Kahn et al, 2006). Rosiglitazone was also associated with an increased risk of fractures in postmenopausal women (Kahn et al, 2008).

DREAM

The 3-year trial DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) found that rosiglitazone significantly reduced the progression to type 2 diabetes by 60% compared with placebo and allowed reversion to normoglycaemia among a large proportion of adults with impaired fasting glucose, IGT, or both (DREAM Trial Investigators, 2006).

PROactive

In the 3-year PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study people with diabetes and cardiovascular disease were randomised to receive pioglitazone versus placebo, in addition to conventional antidiabetes therapy (Dormandy et al, 2005). The primary endpoint, a broad composite that included coronary and peripheral vascular events, showed a trend toward benefit from pioglitazone. The main secondary endpoint consisting of a composite of myocardial infarction, stroke, and death from any cause, showed a significant effect favouring pioglitazone. In the PROactive trial, participants randomised to pioglitazone had a reduced need to add insulin to glucose-lowering regimens compared with those on placebo (Dormandy et al, 2005).

The TZD debate

A meta-analysis published in the *New England Journal of Medicine* in May 2007 reported a significant 43% increase in myocardial infarction (P=0.03) and a borderline significant 64% increase in cardiovascular mortality (P=0.06) for those receiving rosiglitazone as compared with other antidiabetes drugs or placebo (Nissen and Wolski, 2007). An FDA Advisory Committee convened to discuss the meta-analysis and concluded that the use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of myocardial ischaemic events than placebo, metformin or sulphonylureas (Rosen, 2007). The Committee did not recommend that rosiglitazone be removed from the market, but rather that label warnings be added.

In the individual large published trials included in the meta-analysis (specifically DREAM and ADOPT), there were no increases in the rates of myocardial ischaemia or cardiovascular death. The findings have

Page points

1. Data from the ADOPT trial suggest that initial treatment with rosiglitazone slowed the progression to monotherapy failure more effectively than either metformin or glibenclamide, albeit with weight gain.
2. The 3-year DREAM trial found that rosiglitazone significantly reduced the progression to type 2 diabetes by 60% compared with placebo.
3. A meta-analysis published in the *New England Journal of Medicine* in May 2007 reported a significant 43% increase in myocardial infarction and a borderline significant 64% increase in cardiovascular mortality for those receiving rosiglitazone as compared with other antidiabetes drugs or placebo.

Box 4. Meglitinides: key facts and practical considerations.

- Low cost.
- Weight gain can occur.
- Less likely to cause hypoglycaemia than some sulphonylureas (Nathan et al, 2009).
- Reduce HbA_{1c} by 0.5–1.5 percentage points (Nathan et al, 2009).
- May be useful in people with erratic or variable lifestyles (e.g. shift workers), who may take a dose with a meal but omit doses when meals are skipped, or during religious fasting such as Ramadan.

also not been confirmed by studies published subsequent to the meta-analysis including the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study and the interim analysis of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial (Home et al, 2007; ACCORD Study Group et al, 2008).

In the most recent consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), group members unanimously advised against using rosiglitazone (Nathan et al, 2009). Draft NICE guidance anticipated for publication in March 2009 appears to favour pioglitazone (NICE, 2008).

Meglitinides (glinides)

History

The non-sulphonylurea portion of glibenclamide, a benzamido compound termed meglitinide, was shown in the early 1980s to stimulate insulin secretion (Ribes et al, 1981). Repaglinide was introduced in 1998 and nateglinide in 2001.

Mode of action

The meglitinides bind to potassium channels on the cell membrane of pancreatic beta-cells in a similar manner to sulphonylureas, but at a separate binding site. Known as "prandial insulin releasers", these agents stimulate the first-phase of insulin secretion, which is absent or diminished in people with type 2 diabetes. As they are rapidly absorbed and have a fast onset of action, the meglitinides are typically taken 15–30 minutes before main meals. Acting more quickly than the short-acting sulphonylureas, they have a relatively short duration of action.

Indications and licence

The meglitinides are indicated in combination with metformin in people with type 2 diabetes who are not satisfactorily controlled on metformin alone (Daiichi Sankyo UK Limited, 2008; Novartis Pharmaceuticals UK Ltd, 2006). Repaglinide also has a monotherapy licence.

The initial dose should be low and titrated slowly. The recommended starting dose for repaglinide is 0.5 mg, which may be increased to 4 mg (Daiichi Sankyo UK Limited, 2008). The recommended starting dose for nateglinide is 60 mg three times daily before meals, particularly in patients who are near their goal HbA_{1c}. This may be increased to 120 mg three times daily (Novartis Pharmaceuticals UK Ltd, 2006).

Contraindications and side-effects

Like other insulin secretagogues, the meglitinides are capable of producing hypoglycaemia, but because of their short duration of action this may occur less frequently than with the sulphonylureas. The meglitinides have a potential for interaction with drugs that are highly protein bound, such as gemfibrozil. These agents are contraindicated in patients with hepatic disease.

Acarbose

History

Acarbose is the first and only alpha-glucosidase inhibitor and was launched worldwide in 1990.

Mode of action

Acarbose reduces postprandial glucose levels by inhibiting digestion of polysaccharides from the proximal small intestine and is not associated with hypoglycaemia. It is not as effective as the other oral antidiabetes agents at reducing HbA_{1c}, typical reductions range from 0.5–0.8 percentage points (Nathan et al, 2009), and needs to be administered with meals that contain digestible carbohydrates. As carbohydrate absorption occurs distally, no malabsorption or weight loss occurs. However, the delayed absorption causes increased flatulence and gastrointestinal symptoms.

Indications and licence

Acarbose is licensed for the treatment of people with type 2 diabetes, either as first-line therapy

when dietary measures are insufficient, or as an adjunct to conventional oral therapy where glycaemic control is suboptimal (Bayer plc, 2008). It can be used as an add-on therapy in combination with all other antidiabetes agents. Acarbose should be taken with meals starting with a low dose and titrating upwards.

Contraindications and side-effects

Acarbose is contraindicated in people with hepatic impairment and should not be used in those with a creatinine clearance <25 mL/min/1.73 m². The main side effects of acarbose are gastrointestinal, most notably flatulence, which can limit its use. For this reason, a history of chronic intestinal disease is also a relative contraindication (Bayer plc, 2008).

Key evidence

STOP-NIDDM

In the STOP-NIDDM (Study To Prevent Non-Insulin-Dependent Diabetes Mellitus), acarbose reduced the relative risk of developing diabetes by 25% in a population with IGT, compared with placebo (Chiasson et al, 2002). Furthermore, the acarbose-treated group experienced a relative reduction in the risk of cardiovascular events and hypertension (Chiasson et al, 2003).

Treatment algorithms

This article has summarised the mode of action, indications, contraindications, and some practical considerations for the five classes of older blood-glucose lowering agents, but where should these therapies be positioned in the treatment algorithm? Guidance exists in abundance at the local, national, and international level, and is constantly being revised.

Comprehensive guidance is available from the ADA and the EASD (Nathan et al, 2009), and NICE published guidelines on the management of type 2 diabetes for practitioners in England and Wales in May 2008 (NCCCC, 2008; *Figure 2*). A draft NICE guideline incorporating newer therapies is currently awaiting completion (NICE, 2008). At the time of writing, the draft version of this document contains an algorithm on blood glucose lowering therapies, which encourages that treatment decisions at each step are based on considerations of factors such as risk of hypoglycaemia (NICE, 2008).

Despite the availability of such guidance, ultimately treatment choices need to be tailored to the individual.

Box 5. Acarbose: key facts and practical considerations.

- Inexpensive.
- Caution needed in severe renal or hepatic impairment.
- Reduces HbA_{1c} by 0.5–0.8 percentage points (Nathan et al, 2009).
- Use may be limited by gastrointestinal side effects.
- Start with 50 mg once daily and titrate up to a dose of 100 mg three-times daily over 4–8 weeks.
- Not associated with weight gain.

Conclusions

The older blood glucose lowering therapies remain a mainstay in the management of

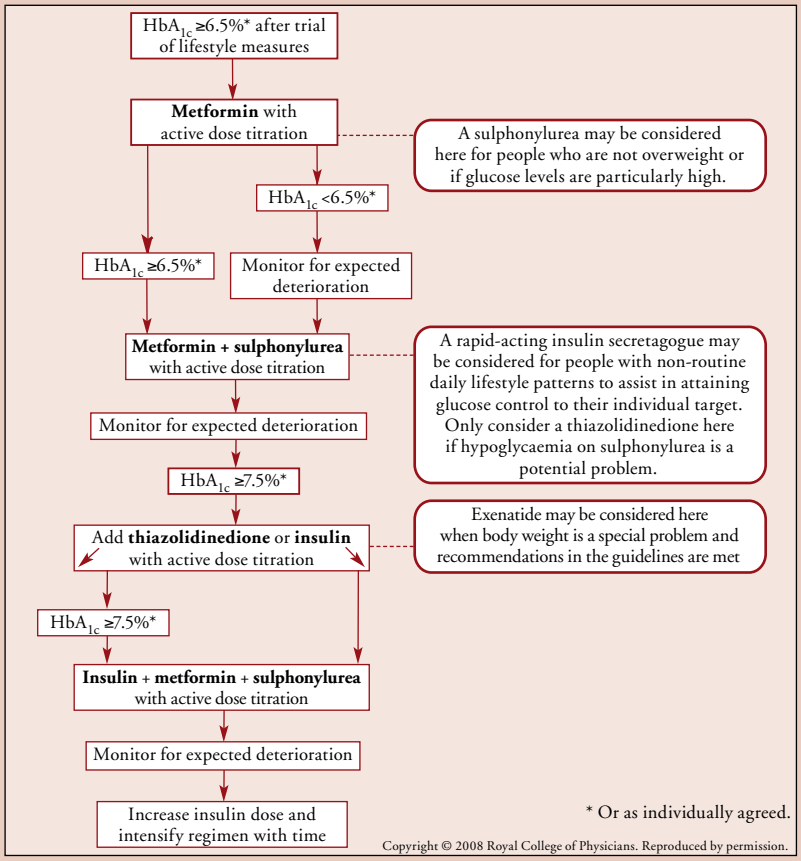

Figure 2. Scheme for the pharmacotherapy of glucose lowering in people with type 2 diabetes, as recommended by NICE. Reproduced from: National Collaborating Centre for Chronic Conditions (2008) with permission from the Royal College of Physicians, 2008.

Box 6. Case study.

Narrative

Meera is a 43-year-old lady of South Asian origin, who works shifts (including nights) in a clothing factory. She has had diabetes for 7 years. She finds it difficult to attend clinic appointments, and has not been seen in the surgery for some time. Meera is married, and her husband is unable to work due to back problems. She does not smoke or drink alcohol.

Her oral blood glucose lowering medication was initially prescribed by her former GP and the regimen remains unchanged since she moved to the current practice 2 years ago. She currently takes metformin 850 mg three-times daily, and glibenclamide 5 mg three-times daily. She attends the surgery because she was taken ill at work with dizzy spells, and had to be sent home. Her employer is not sympathetic to her illness.

Her GP finds no abnormalities on examination, and blood test results reveal an HbA_{1c} level of 7.1%, an HDL-cholesterol level of 0.8 mmol/L and a total cholesterol of 4.6 mmol/L. Her BMI is 27 kg/m^2, her waist circumference is 86 cm, and her blood pressure is 122/77 mmHg.

Discussion

We need to know whether Meera is taking her medication as prescribed: shift workers find it very difficult to stick to three-times daily dosing regimens. More information about her dizzy spells is needed, as she may be experiencing hypoglycaemic episodes. For example, what are the exact symptoms?; how do they relate to meals and activity?; is there sweating? We also need to find out about her role in the home. Is she having to cook her husband's meals, and does she eat with him?

In terms of blood glucose lowering therapy, she may benefit from a simplified regimen. Metformin could be given twice-daily instead of three times per day. Glibenclamide has a long duration of action, whereas a prandial insulin releaser such as nateglinide may instead be helpful if she has irregular eating schedules, and may reduce any tendency to hypoglycaemia. A thiazolidinedione could be considered, in view of the presence of some features of the metabolic syndrome, and the low incidence of hypoglycaemia. Furthermore, in some South Asian cultures, insulin carries negative connotations; if her control subsequently deteriorates, triple oral therapy may be appropriate before discussing insulin initiation.

hyperglycaemia in type 2 diabetes. Their differing mechanisms of action provide the opportunity for combination therapy, targeting both underlying insulin resistance and reduced endogenous insulin secretion. In order to make an appropriate choice of agent for a particular individual, a consideration of a person's lifestyle, diabetes, comorbidities and preferences should be balanced against the key attributes of each drug (*Box 6* provides an exemplar case study).

In striving to manage hyperglycaemia in type 2 diabetes, data from the UKPDS (UKPDS Group, 1998a; UKPDS Group, 1998b), ACCORD (ACCORD Study Group, 2008), ADVANCE (ADVANCE Collaborative Group, 2008), and the VADT (Duckworth et al, 2009), as well as the UKPDS update (Holman et al, 2008), suggest that early, stepwise treatment, with avoidance of hypoglycaemia should be our aim. ■

Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**: 2545–59

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"The older blood glucose lowering therapies remain a mainstay in the management of hyperglycaemia in type 2 diabetes."

CPD module

CPD module

Online CPD activity

Visit www.diabetesandprimarycare.co.uk/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learned in practice.

1. **A 53-year-old woman attends the practice nurse with a non-healing leg ulcer. A family history of diabetes is elucidated and she admits to feeling tired. Her BMI is 33 kg/m^2. Investigations reveal that she has fasting glucose levels of 11.5 and 13.3 mmol/L on two occasions, and an HbA$_{1c}$ level of 8.3%, and her liver and renal function are normal. According to the 2008 NICE guidance on type 2 diabetes, and assuming that lifestyle approaches have not been successful, what is the SINGLE most appropriate treatment step?**
   A. Gliclazide, titrating to 160 mg twice daily.
   B. Metformin, titrating to 1 g twice daily.
   C. Extended release metformin, titrating to 1 g twice daily.
   D. Rosiglitazone, titrating to 8 mg daily.
   E. Vildagliptin 100 mg daily.

2. **A 63-year-old woman was diagnosed with type 2 diabetes 3 months ago. There has been a poor response to lifestyle measures. Her HbA$_{1c}$ is 8.7%, her fasting glucose levels average 13 mmol/L and her estimated glomerular filtration rate is 37 mL/min/1.73 m^2, with a creatinine level of 167 µmol/L. Her BMI is 34 kg/m^2. According to the 2008 NICE guidance on type 2 diabetes, what is the SINGLE most appropriate treatment step?**
   A. Gliclazide, titrating to 160 mg twice daily.
   B. Metformin, titrating to 2 g daily.
   C. Extended-release metformin, titrating to 1 g twice daily.
   D. Rosiglitazone, titrating to 8 mg daily.
   E. Vildagliptin 100 mg daily.

3. **An 87-year-old lady who resides in sheltered accommodation has a 23-year history of type 2 diabetes. Care assistants report that they find her confused when they bring her lunch. Her medication is gliclazide 80 mg four-times daily. Her last recorded HbA$_{1c}$ level was 6.6%. What is the SINGLE most appropriate next management step?**
   A. Change gliclazide to metformin.
   B. Change gliclazide to pioglitazone.
   C. Reduce gliclazide dose to 80 mg twice daily.
   D. Start basal–bolus insulin therapy.
   E. Stop gliclazide.

4. **A 71-year-old woman with type 2 diabetes is being considered for escalation of her blood glucose lowering therapy and it has been agreed to start her on a thiazolidinedione. Apart from avoiding its use in those with previous or current cardiac failure, which ONE of the following is the most relevant consideration before starting this therapy?**
   A. History of depression.
   B. History of cardiac arrhythmias.
   C. A known fracture risk.
   D. Reducing visual acuity.
   E. Current use of metformin.

5. **When considering mode of action, which of the following classes of agent produces its glucose-lowering effect primarily by interrupting carbohydrate metabolism in the gastrointestinal tract. Select ONE option only.**
   A. The thiazolidinediones.
   B. Metformin.
   C. Repaglinide.
   D. The sulphonylureas.
   E. Alpha-glucosidase inhibitors.

6. **Which of the following statements about metformin is true? Select ONE option only.**
   A. It should be stopped in a patient who has had a myocardial infarction.
   B. It commonly causes hypoglycaemia.
   C. It increases the absorption of glucose from the gastrointestinal tract.
   D. It is normally started at a dose of 2 g daily.
   E. It cannot be used in conjunction with long-acting analogue insulins.

7. **When considering metformin which ONE of the following statements is untrue? Select one option only.**
   A. It acts by increasing hepatic glucose production.
   B. It acts by improving peripheral sensitivity to insulin in the muscle and adipose tissue.
   C. It was associated with a reduction in the incidence of myocardial infarction in the UKPDS.
   D. It does not cause weight gain.
   E. It may be associated with weight loss.

8. **Which one of the following is not a recognised effect or fact associated with the use of sulphonylureas? Select ONE option only.**
   A. Hypoglycaemia.
   B. Weight gain.
   C. Residual beta-cell function required for efficacy.
   D. Depressive illness.
   E. Rapid reductions in HbA$_{1c}$ are achievable.

9. **Which of the following statements is not true of the meglitinide class of drugs. Select ONE option only.**
   A. They are classed as "insulin sensitisers".
   B. They have a shorter duration than sulphonylureas.
   C. They may be particularly suitable for people with erratic or variable lifestyles.
   D. They act by reducing fasting hyperglycaemia.
   E. On the molecular level, they have a similar method of action to the sulphonylureas.

10. **When considering the effects of thiazolidinediones, which of the following statements is true? Select ONE option only.**
    A. They are "insulin sensitisers".
    B. Their use is associated with visceral fat deposition.
    C. They increase hepatic glucose production.
    D. They can be used in people with hepatic impairment.
    E. They are not licensed for use in a triple oral therapy regimen.