

The mechanism of action of oral antidiabetic drugs: A review of recent literature



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Type 2 diabetes mellitus (DM) is a disorder that is placing an increasing burden on health service delivery worldwide. Consequently, it has become increasingly important that physicians who treat such patients have a good knowledge of antidiabetic drugs that are currently available or will come onto the market. This article presents an overview of all the major drug classes as well as some information on pharmacokinetics, pharmacodynamics, side-effect profiles and indications for use.

Type 2 diabetes mellitus (DM) is a disorder characterised by insulin resistance and a progressive decline in pancreatic beta-cell function associated with increasing hyperglycaemia. Defective beta-cell function occurs early and can be detected in individuals with impaired fasting and/or post-prandial glucose levels (the so-called 'pre-diabetics'). The United Kingdom Prospective Diabetes (UKPD)¹ study indicated that by the time type 2 DM is diagnosed, individuals have already lost up to 50% of their beta-cell function. The decline in function proceeds at 6% per year, which is 20 times greater than that explained by normal ageing.

The targets for glycaemic control as set by the American Diabetes Association (HbA_{1c} <7%)² and the American Association of Clinical Endocrinologists (HbA_{1c} <6.5%)³ sometimes appear daunting and unattainable. It is therefore of the utmost importance to have an excellent understanding of the mechanism of action of these drugs in order to optimise patient therapy. The aim of this article is to present an overview of all the available oral antidiabetic drugs according to the different classes, their mechanisms of action and pharmacological profiles, and to assist physicians to make the correct choice for their patients.⁴

Insulin secretagogues

Sulfonylureas (glibenclamide, gliclazide, glipizide, glimepiride)

The sulphonylureas (SUs) were initially developed in the 1920s and have become indispensable in the

management of type 2 DM. The mechanism of action involves a direct secretory effect on the pancreatic islet beta-cells. Adenosine triphosphate (ATP)-sensitive potassium channels (K⁺_{ATP}) of the beta-cells play an essential role in the release of insulin and consist of two components: a pore and a regulatory subunit (SUR-1).

The sulphonylureas act to enhance the sensitivity of the beta-cell to glucose and, when bound to the transmembrane sulphonylurea receptor (SUR-1), mediate the closing of the potassium-sensitive ATP channels on the cell membrane. Cellular efflux of potassium is reduced and membrane depolarisation takes place. Calcium influx is mediated by the opening of voltage-dependent Ca²⁺-channels that promote the release of pre-formed insulin granules which lie just adjacent to the plasma membrane (Fig. 1).⁵

Sulphonylureas enhance the so-called first phase of insulin secretion whereby the insulin-containing granules close to the plasma membrane are released as well as the so-called second phase of insulin release a few minutes later when more insulin granules are translocated from the cytoplasm to the beta-cell membrane and released by ATP-dependent exocytosis.⁶ Hypoglycaemia can occur because these drugs potentiate the release of insulin even when glucose concentrations are below the normal threshold for glucose-stimulated insulin release (<5 mmol/l).^{7,8}

Sulphonylureas are well absorbed after oral administration and reach peak plasma concentrations within 2 - 4 hours.⁹ Food ingestion appears to have

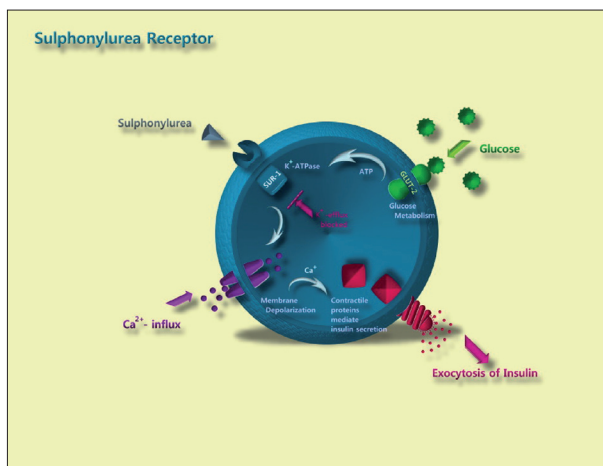


Fig. 1. The sulphonylurea receptor.

very little effect on their efficacy, but it is nevertheless advised that they be taken at least 15 - 20 minutes before a meal.

Glibenclamide is considered an intermediate-acting drug (12 - 24 hours) with active metabolites of which approximately 50% are eliminated by the liver.^{10,11} Gliclazide (Diamicon) also has a duration of action of 12 - 24 hours, but up to 65% of active metabolites are excreted mainly by the kidneys.¹² Glimepiride has a duration of action of about 24 hours and is eliminated by the liver.¹³ It is very important to keep in mind that since all sulphonylureas are highly bound to plasma proteins, they can potentially interact with other protein-bound drugs, e.g. warfarin. Displacement from plasma proteins because of drug interactions has been implicated as a cause of severe SU-induced hypoglycaemia.

Sulphonylureas remain a popular choice for first-line therapy in a type 2 diabetic patient who has failed on non-pharmacological measures and is non-obese (although metformin is now recommended as first-line therapy for all type 2 diabetics).¹⁴ They can be used in combination with other classes of antidiabetic drugs except other secretagogues (including the meglitinides). They can also be used in combination with longer-acting insulin as part of the daytime-sulphonylurea-night-time-insulin regimen.¹⁵ Starting with a low oral dose, dosages can be up-titrated at intervals of 2 - 4 weeks to achieve optimal glycaemic control.

The use of sulphonylureas is contraindicated in type 1 DM, pregnancy (class C indication for use), and renal and liver disease. The last two conditions drastically alter the half-life of these drugs and can increase the plasma concentrations up to 3 times, which contributes greatly to increased risk of hypoglycaemic events. It is not advisable to use these drugs once the glomerular filtration rate (GFR) falls to below 40 ml/min.^{8,11}

It is important to note that the receptor-specific binding characteristics of all the different sulphonylureas differ. Concern has been expressed that these drugs may aggravate angina symptoms in diabetic patients with existing coronary artery disease (CAD).^{16,17} Sulphonylureas also bind SUR-2 A and B receptors in the cardiac muscle, initiating contraction at high concentrations. Another issue is the fact that the SUR-2 associated K⁺-channel in the heart mediates protective ischaemic preconditioning of cardiac muscle, and if this channel closes because of sulphonylurea stimulation, the mortality of diabetic patients on sulphonylureas with myocardial infarctions may increase. Use of the sulphonylurea types that bind the SUR-2 A and B receptors (glibenclamide, glipizide, glimepiride) should be avoided in high-risk patients suspected of having significant CAD.^{18,19}

When sulphonylureas are used as monotherapy with strict diet, a further reduction in fasting glucose of 2 - 4 mmol/l and a reduction in HbA_{1C} levels of 1 - 2% can be expected.²⁰ Efficacy of combination therapy depends on which drug is used. With the addition of metformin or any thiazolidinedione, a maximum additional reduction of 1% can be achieved (and 0.5% in the case of α -glucosidase inhibitors).²¹

Side-effects that have been described include hypoglycaemia, weight gain (1 - 4 kg over 6 months), skin reactions, acute porphyria and, rarely, hyponatraemia.^{15,16} There have been reports in the literature of glimepiride-induced acute cholestatic hepatitis.²² In patients with overt liver synthetic dysfunction, glimepiride should also be avoided owing to the increased risk of hypoglycaemia (glimepiride metabolised in the liver).

Rapid-acting prandial insulin releasers (repaglinide, nateglinide)

In the natural history of type 2 diabetes, a blunted response of the first phase of glucose-stimulated insulin release has been observed. An initial surge of insulin is necessary to suppress hepatic gluconeogenesis in the postprandial period. If this mechanism fails, postprandial hyperglycaemia is worsened and the HbA_{1C} levels are adversely affected. The meglitinides were developed to address this problem. Taken orally shortly before a meal, they can stimulate rapid, short-lived insulin release. The mechanism of action of prandial insulin releasers indicate that they bind to the SUR-1 receptor in much the same way as the sulphonylureas. The short half-life of these drugs potentiates the effect of the first phase of insulin secretion, but the effect on the second phase is not sustained.²³

Repaglinide's pharmacokinetic profile shows that it is rapidly absorbed after oral intake and can reach peak concentrations within 1 hour (t_{1/2} = 0.6 hours).

The duration of action is 4 - 5 hours; the drug is metabolised by the liver and excreted in both faeces and urine.²⁴ Nateglinide has $t_{1/2} = 1.5$ hours and duration of action of 5 - 6 hours. In contrast to repaglinide, this drug has active metabolites. Excretion is in bile and urine.²⁵

Repaglinide can be used in patients who do not achieve glycaemic control on diet and lifestyle measures alone or who live irregular lifestyles where meals are missed or taken irregularly. These drugs should be taken immediately before meals.^{26,27} The lower risk of hypoglycaemia, compared with a sulphonylurea, makes these drugs an attractive choice in elderly patients; they may cause minimal weight gain.

Monotherapy causes a reduction in HbA_{1C} of 1 - 2% and, when combined with metformin, the reduction can be pushed up by 1.5%.²⁸ These drugs can also be combined with other oral hypoglycaemic agents (excluding SUs) with added benefit.²⁴

Insulin sensitisers

Biguanides (metformin)

Metformin has been available since the 1950s. Its historic roots and origin can be traced back to the guanidine-rich *Galega officinalis* (goat's rue or French lilac) which has traditionally been used in Europe to treat diabetes. Metformin has a variety of clinical actions that extend beyond just the glucose-lowering effects such as weight reduction, improving lipid profiles and vascular effects, which includes improving endothelial function, as well as decreasing PAI-1 levels.⁴

The molecular mechanisms of action have not as yet been clearly established. However, it is thought that insulin sensitivity is improved and mediated via modification of post-receptor signalling in the insulin pathway. A protein, adenosine 5'-monophosphate protein kinase, has been identified as a possible target of metformin.^{29,30}

The mainstay of action of this class of drug can be attributed to its hepatic effects. Hepatic sensitivity to insulin is increased, thereby reducing gluconeogenesis as well as glycogenolysis, which contributes to the post-prandial plasma glucose-lowering effects. Skeletal muscle and adipocytes undergo up-regulation of the insulin-sensitive GLUT-4 and GLUT-1 transporters to the cell membranes, thereby increasing glucose uptake.³¹ Glucose metabolism in the splanchnic bed also increases. Further metabolic effects include suppression of fatty acid oxidation as well as triglyceride lowering.^{31,32}

Metformin is quickly absorbed and fully eliminated in the urine via tubular secretion. Therefore it is prudent

to avoid this drug in patients with impaired renal function. Metformin should be discontinued prior to contrast studies, e.g. angiographic evaluations, since it has been implicated in the development of contrast-induced nephropathy. The iodinated contrast media compete with metformin for tubular secretion, and caution is necessary if the administration of competing substances is required. Since metformin is not bound to plasma proteins and is not metabolised, it does not interfere with co-administered drugs. In patients with normal renal function, the plasma $t_{1/2}$ is 2 - 5 hours, with 90% of the dosage eliminated within 12 hours.

Biguanides are generally considered the drugs of choice in obese type 2 diabetics. Metformin can be used in combination with any other class of oral antidiabetic drug or with insulin. Metformin is also used in the treatment of polycystic ovarian syndrome (PCOS) to improve insulin sensitivity and to lower circulating androgen levels. It also improves ovulation and menstrual cyclicity. The USA's Food and Drug Administration still considers this an unlicensed indication of this drug in the absence of diabetes. The American Association of Clinical Endocrinologists recommends that metformin be considered as the initial intervention in most women with PCOS, particularly those who are obese and overweight.³³ The use of metformin for gestational diabetes seems to be safe, as indicated by the recently published MiG study.³⁴

Contraindications include the presence of underlying impairment of renal function, conditions predisposing to hypoxia or reduced perfusion because of the increased risk of lactic acidosis, liver disease, alcohol abuse and a history of a previous episode of lactic acidosis.

When used at optimal dosages, the decrease in fasting glucose levels is estimated at 2 - 4 mmol/l, with a drop in HbA_{1C} levels of 1 - 2%. The UKPDS study also showed that overweight patients started on biguanides had a lower myocardial infarction risk (of 39%) than patients on conventional therapy.¹ The mechanism of the cardioprotective effects is still unclear.

Side-effects can include lactic acidosis. Metformin increases lactate production in the splanchnic bed and portal venous system due to a reduction in the activity of pyruvate dehydrogenase enzyme, thereby shifting the metabolism towards the anaerobic spectrum. However, the incidence of metformin-induced lactic acidosis is extremely rare, with only 0.03 cases per 1 000 patient-years reported in the literature. Abdominal discomfort and diarrhoea are the most frequent side-effects. Vitamin B₁₂ deficiency owing to decreased GIT absorption can occur.³⁵

Thiazolidinediones (pioglitazone, rosiglitazone)

With the introduction of this new class of drug in 1997, the world has watched the peroxisome proliferator activated receptor (PPAR)- γ agonists with anticipation. The net effect of these drugs results from stimulation of a nuclear PPAR- γ that regulates the transcription of genes culminating in an increase in insulin sensitivity. Troglitazone, the forerunner drug, was withdrawn in 2000 following reports of fatal hepatotoxicity, and the future of rosiglitazone currently hangs in the balance, owing to a possible increased risk of myocardial infarction and cardiovascular-related deaths.³⁶

Thiazolidinediones (TZDs) mediate their function through binding to the PPAR- γ receptor that is expressed predominantly in adipocytes (Fig. 2). It is expressed to a lesser extent in muscle and liver tissue. Binding of the PPAR receptor in turn mediates binding to the retinoic-X receptor (RXR-receptor). This heterodimer then binds to a nuclear response element which then switches on gene transcription. Many of the genes that are activated play a central role in carbohydrate and lipid metabolism. TZDs, like metformin, require the presence of insulin to mediate a blood glucose-lowering effect. Interestingly, the thiazolidinediones also suppress the expression of TNF- α by adipocytes. The pharmacokinetics of these drugs indicates that both rosiglitazone and pioglitazone are rapidly absorbed after a meal, reaching peak concentrations within 1 - 2 hours. Both drugs undergo hepatic metabolism, with rosiglitazone excreted mainly in urine and pioglitazone in bile. Although rosiglitazone and pioglitazone are metabolised by CYP 2C8 and CYP 3A4 respectively, no major drug interactions have been reported.

This class of drug can be used as monotherapy in obese as well as non-obese patients who have failed other conservative measures. TZDs can be used in combination with metformin and sulphonylureas. The use in combination with insulin is prohibited in Europe because of the increased risk of weight gain in the form of adipogenesis and fluid retention. The use of TZDs is contraindicated in acute liver disease owing to the increased risk of hepatotoxicity. Since they decrease hepatic glucose output, the concern exists that they could possibly aggravate hypoglycaemia.

The effects of the glitazones on cardiovascular morbidity and mortality remain a topical issue. It seems, from the literature, that pioglitazone especially has a more favourable effect on major cardiovascular outcomes. The PROactive study showed a significant reduction of 16% in the main secondary endpoints of all-cause mortality.³⁷ It is thought that the beneficial effects of the glitazones extend beyond their influence on glycaemic control through so-called

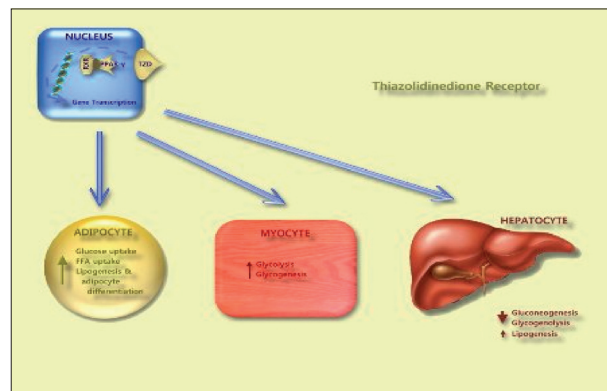


Fig. 2. The PPAR- γ receptor.

pleiotropic effects. These include an increase in coronary flow reserve, a decrease in intima media thickness, an improvement of endothelial function as well as a decrease in inflammatory and pro-coagulant biomarkers.^{38,39} The use of TZDs in patients with New York Heart Association (NYHA) class III or IV heart failure is not recommended in view of the side-effects of fluid retention and weight gain. The pathophysiology of TZD-related fluid retention includes several potential mechanisms such as increased vascular permeability, decreased urinary sodium excretion, increased sympathetic tone and altered interstitial ion transport. It has also been postulated that TZDs may actually unmask previously undiagnosed cardiac dysfunction owing to their effects on salt and water retention.⁴⁰ The initial dose should be very low in patients who have risk factors for heart failure. The concurrent use of these drugs in combination with insulin is not recommended as weight gain can be aggravated.⁴¹ Safety of the glitazones in pregnancy and lactation has not yet been established. In some studies, TZDs have demonstrated a beneficial effect on ovulation in patients with PCOS. However, their use is not recommended in this condition, since these drugs display gene activity that may be harmful in early pregnancy.

Another complication related to the use of this class of drug is that of TZD-induced low-formation osteoporosis. Already in 2006, evidence of an increased fracture risk with rosiglitazone emerged as the data of the ADOPT trial were published.⁴² These trial data reported an increased fracture risk in women but not in men. Significant bone loss with an increased fracture risk only became noticeable after 12 months on treatment. Following this trial, the manufacturers of pioglitazone reviewed their clinical trial databases and, in 2007, reported an increase of fracture risk in females treated with pioglitazone, but not in men. It was also stated that the fractures occurred mostly in the distal upper limb or distal lower limb.⁴³ The TZD effect on bone appears to be an inhibition of osteoblast differentiation, with a resultant negative effect on cortical bone formation without a change in bone resorption. An increase in

marrow adiposity accompanies bone loss because of rosiglitazone treatment. It appears that activation of PPAR- γ increases the allocation of stem cells towards adipocytes at the expense of osteoblasts.⁴⁴ There are no studies on treatments that may prevent bone loss induced by TZDs.⁴⁵ Treatments that increase bone formation are currently limited to parathyroid hormone (PTH) and strontium ralenate, and could potentially be used to target TZD-induced osteoporosis.

These drugs have been shown to effectively lower the HbA_{1C} by $\pm 0.5 - 1.5\%$. Side-effects that are commonly experienced include weight gain (around 1 - 4 kg over 6 - 12 months), oedema with worsening of cardiac failure, liver toxicity and anaemia (most likely due to haemodilution).⁴⁶

Glucosidase inhibitors (acarbose)

Acarbose was the first glucosidase inhibitor and was introduced to the market in the early 1990s. This class of drug has the advantage of reducing postprandial hyperglycaemia without associated weight gain. Its usage is at present hampered by unfortunate gastrointestinal side-effects despite a good safety record. The α -glucosidase inhibitors inhibit the activity of the glucosidase enzymes which are present in the brush border of enterocytes in the intestinal villi. Disaccharide and oligosaccharide cleavage is prevented with a net decrease in intestinal carbohydrate absorption. Overall, the α -glucosidase inhibitors reduce postprandial insulin concentrations through the attenuated rise in postprandial glucose levels.

Less than 2% of the drug is absorbed. It is broken down by intestinal amylases and certain intestinal bacteria. Some degradation products are taken up and subsequently eliminated in the urine. The drug should be taken with the first bite of food during a meal and not more than 15 minutes after the start of the meal.

This drug is ideal for initiation of pharmacotherapy in type 2 diabetic patients. The STOP-NIDDM trial showed that acarbose can be utilised in the prevention of type 2 diabetes by delaying progression from an impaired fasting glucose state to overt type 2 diabetes.^{47,48} Combination therapy with any other antidiabetic agent is possible.

The use of these drugs is contraindicated in pregnancy and breastfeeding. Efficacy measures show that postprandial glucose levels can be lowered by 1 - 4 mmol/l. An average decrease in HbA_{1C} of 0.5 - 1.0% can be expected. Side-effects include flatulence, abdominal discomfort and diarrhoea, but tolerance of the side-effects quickly develops. Hypoglycaemia can occur only if used in conjunction with a sulphonylurea or insulin.

New drug modalities

Incretins (exendin-4, liraglutide, vildagliptin, sitagliptin)

The small intestine secretes glucagon-like peptide-1 (GLP-1) as well as glucose-dependent insulinotropic polypeptide (GIP, previously called gastric inhibitory peptide) in response to food intake. These hormones stimulate insulin secretion, insulin gene expression and pancreatic beta-cell growth. Furthermore, they mediate the incretin effect which augments insulin secretion following oral administration of glucose. The GLP-1 molecule is subject to rapid degradation by the DPP-IV (dipeptidyl peptidase) enzyme.

Patients with type 2 diabetes have greatly impaired or absent incretin-mediated insulin secretion due to a decrease in the level of GLP-1 which leads to a decrease in glucose-dependent secretion of insulin by the pancreatic beta-cells.^{49,50}

Several therapeutic strategies are currently undergoing clinical trials, namely:

- enzyme-resistant GLP-1 analogues (exendin-4)
- albumin-bound GLP-1 derivatives (liraglutide)
- DPP-IV enzyme inhibitors (vildagliptin, sitagliptin).

Exendin-4 (exenatide)

This molecule was originally isolated from the venom of the Gila monster (*Heloderma* lizard species) and has a synthetic version (exenatide). The synthetic 39-amino acid peptide sequence overlaps with that of GLP-1, but has a longer half-life than native GLP-1. This 'incretin mimic' improves glycaemic control mainly by stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon secretion. It also delays gastric emptying, reduces food intake and facilitates weight loss.

It is given as a twice-daily subcutaneous injection and can decrease HbA_{1C} levels by a further 1% if given in combination with other drugs. Once-daily injections did not achieve satisfactory control in clinical trials.⁵¹

Liraglutide

This drug is currently in phase III of clinical development. The results look extremely promising. In June 2007, a 26-week study was conducted in which liraglutide was compared with insulin-glargine. This formed part of the greater liraglutide effect and action in diabetes (LEAD) programme. At the end of the 26 weeks, the liraglutide group showed that >50% of patients reached the HbA_{1C} goal of <7% as well as an average weight loss of 3.5 kg. This drug, given as a once-daily subcutaneous injection, has a plasma half-life of 12 hours.⁵²

Vildagliptin

This drug is taken in oral form as a once-daily dosage. Inhibition of dipeptidyl peptidase-IV

(DDP-IV) stimulates the secretion of insulin in a glucose-dependent fashion, so minimising possible hypoglycaemic side-effects. Inhibition of DDP-IV is dose-dependent. Recent data suggest restorative effects on pancreatic islet cells, thereby fuelling the hope that the DDP-IV inhibitors could potentially slow or reverse the course of beta-cell failure.⁵³⁻⁵⁵

Sitagliptin

This drug is also a DDP-IV inhibitor and can be used as monotherapy in type 2 diabetes or in combination with metformin, the SUs or the TZDs if the existing regimen no longer provides adequate glycaemic control. It has not yet been studied in combination with insulin. Sitagliptin is taken orally and has been shown to reduce HbA_{1C} levels by 0.6 - 1%.

Amylin analogues (Pramlintide)

Human amylin is a 37-amino acid glucoregulatory peptide that is co-secreted with insulin by the pancreatic beta-cells. Pramlintide, a synthetic analogue, exerts its effect by slowing down gastric emptying and increasing satiety. Post-prandially, it decreases glucose levels and reduces the re-introduction of glucose in the circulation.

Pramlintide is administered as a subcutaneous injection immediately before a meal. The peptide undergoes renal clearance and has a t_{1/2} of 50 minutes. It is well tolerated and is not associated with the risk of hypoglycaemia.^{56,57}

Conclusion

The challenge of treating type 2 DM grows by the day as the number of patients increase. Therefore, a good understanding of the available treatment modalities is of great value. As the pathogenesis of diabetes becomes clearer, exciting new targets for drug therapy will be identified, which provide physicians with more 'fire power' and treatment options in the fight against this disease.

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