Oral hypoglycaemic drugs and newer agents use in Type 2 diabetes mellitus

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Abstract

We have reviewed the use of oral agents in the management of Type 2 diabetes, together with their pharmacological mechanisms, indications, side effects and contra-indications. The principal oral agents available for use include metformin, sulphonylureas, non-sulphonylurea secretagogues (meglitinides), thiazolidinediones, and α-glucosidase inhibitors. More recently, DPP-IV inhibitors and glucagon-like peptide-1 agents have been registered for use in the United States and in Europe. They await Medicines Control Council registration for use in South Africa. This article will discuss the various oral hypoglycaemic agents, together with the newer modes of therapy, which are soon to become available in our therapeutic armamentarium in South Africa.

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Introduction

Diabetes is a chronic progressive disorder, with multiple biological defects, which necessitates the use of a range of different classes of drugs in order to optimise disease control over the patients' life span. To date there have been oral drug classes such as the biguanides, sulphonylureas, and injectable insulin options such as human and analogue insulin, which have become household names in the treatment of diabetes. New treatment options that target the incretin system are now available. These now widen the choices for commencing treatment for Type 2 diabetes. We can choose the appropriate drugs for optimal control of diabetes targeting specific pathophysiological defects. It is important to understandthe mechanism of action of these drugs to fully comprehend the mode and extent of glucose control that can be achieved as well as the side effects that could be anticipated.

We have previously discussed the pathophysiological defects that play a role in the aetiopathogenesis of Type 2 diabetes in an earlier article[1] and are summarised here:

1. Progressive insulin resistance
2. ß-cell failure and
3. Hyperglucagonaemia

This understanding is of vital importance in approaching the correct therapeutic management of the disease.

The present article will discuss the various oral hypoglycaemic agents, together with the newer modes of therapy, which are soon to become available in our therapeutic armamentarium in South Africa.

Treatment of Type 2 diabetes is aimed at lowering insulin resistance and restoring the function of pancreatic α- and ß-cells. Over time, as ß-cell dysfunction worsens progressively, there comes a need for insulin replacement therapy.

Upon diagnosis of Type 2 diabetes, the patients are advised on the central importance of lifestyle interventions such as following an appropriate diet, and the performance of regular physical exercise. This has to be adhered to throughout the course of the disease, regardless of the therapy type used. The therapeutic goal of diabetes is to achieve an HbA_{1c} value of at least 6.5–7.0%. Both fasting and postprandial glucose control need to be addressed in order to achieve this target. Oral diabetic agents are used as monotherapy or combination therapy depending on the ß-cell function reserve and level of insulin resistance.

Pharmacotherapy

Oral antidiabetic (OAD) agents that will be discussed include:

- Biguanides
- Sulphonylureas
- Meglitinides
- Thiazolidinediones
- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase IV (DPP-IV) inhibitors
- Glucagon-like peptide-1 (GLP-1) analogues

Biguanides

There have been a few biguanides available commercially, the principal ones being metformin and phenformin. For many years now the use of phenformin has been discontinued primarily because of its potential for producing severe life threatening lactic acidosis.[2]

Metformin has been available over the last four decades. It has a number of postulated mechanisms for lowering plasma glucose:

- It decreases fasting plasma glucose (FPG) by reducing hepatic gluconeogenesis[31];
- It improves insulin sensitivity in peripheral tissues;

- It decreases intestinal absorption of glucose, reducing post-prandial glucose;
- It has more recently been shown to stimulate GLP-1 production from the gastrointestinal tract which, inter alia, suppresses pancreatic α-cell function, reducing serum glucagon and further reducing fasting hyperglycaemia.

Since metformin has no direct stimulatory effect on the ß-cell, it does not cause hypoglycaemia or weight gain. In fact, it induces mild to modest weight loss by suppression of appetite with a reduction in net caloric intake due to appetite suppression, and a reduction in hyperinsulinaemia related to insulin resistance. In most patients one finds that in order to maintain glycaemic control, further up-titration of dose is required, probably in keeping with increasing insulin resistance.

Metformin may reduce FPG by about 3–4 mmol/L, and HbA_{1c} by 1.5%.[3,4] The maximum reduction of HbA_{1c} achieved with any combination of oral antidiabetic drugs is 3%–4 %.[32]

Metformin is initiated at 500 mg orally once or twice daily with or after meals to minimise GI effects.[10] Metformin should be started at 500 mg orally once daily with the evening meal, and beneficial effects can be seen within 1 week. The dose can be titrated every 2–4 weeks up to 2000 mg daily.[2] It can be prescribed in doses of up to 1 gm bd. Metformin is considered a first-line agent in all algorithms and is particularly useful in those who are obese, or have insulin resistance.

Effects on lipids

Metformin has been shown to decrease the low-density lipoprotein (LDL) and triglyceride levels (TG) by about 0.12–0.26 mmol/L and it has minimal effect on high-density lipoprotein (HDL) levels.[3,5] In the UKPDS and other more recent trials, a reduction in diabetes-related end-points, deaths, and myocardial infarctions with metformin compared to diet therapy has been shown.[6,7] Metformin can be combined with all the classes of oral antidiabetic agents, with insulin, and with the newer DPP-4 inhibitors and the GLP-1 mimetics and analogues. It shows synergism with all the different classes of agents.

Side effects

- Up to a third of patients on metformin experience gastrointestinal (GI) side effects, such as nausea, diarrhoea, abdominal discomfort, and a metallic taste, which can be reduced by titrating the dose up slowly and by taking medication with or after meals.[2]
- The reported incidence of lactic acidosis with metformin is rare at 0.03 per 1000 patient-years of use. It is fatal in 30% to 50% of cases.[8] A recent systematic review found no cases of lactic acidosis associated with metformin use in Type 2 diabetes when contraindications were observed.[9] At high doses, especially in renal failure, it accumulates in mitochondria, inhibits oxidative phosphorylation and causes lactic acidosis (which can be further potentiated by alcohol).
- Metformin can interfere with vitamin B12 absorption and may lower serum vitamin B12 levels through unknown mechanisms, but is rarely of clinical significance. Anaemia has been observed in 7% of people in clinical trials. It appears to be rapidly reversible with discontinuation of the drug. It is recommended to monitor haematological parameters.[8]

Contra-indications

Metformin is contraindicated in people with the following risk factors for lactic acidosis:

- Renal (serum creatinine ≥ 130 mmol/L in men, or ≥ 120 mmol/L in women)
- Hepatic impairment
- Respiratory insufficiency
- Severe infection
- Alcohol abuse
- Heart failure requiring pharmacological therapy
- Metformin should also be used with caution in elderly people (older than 80 years) with reduced lean body mass. It is recommended to monitor renal function upon initiating metformin and at least annually thereafter.[10]
- Any patient undergoing radio-contrast studies should have metformin withheld one day before the study and 48 hours after the study to avoid any potential lactic acidosis.[29]

Sulphonylurea secretagogues

The sulphonylurea (SU) group of drugs has been available for the last 50 years. All of them (glibenclamide, glipizide and gliclazide) have a similar mechanism of action that is mediated by inducing closure of the ATP-sensitive potassium (K+) channels. The intracellular retention of K+ changes the membrane potential resulting in depolarisation of the ß-cell, and opening of the voltage-dependent calcium channels. This facilitates movement of Ca++ into the cell, stimulating exocytosis of insulin into the circulation.[30]

Traditionally, sulphonylureas are classified into first- and second-generation depending on their duration of action. The latter group, in general, has a greater potency and improved safety.

Examples of the first-generation SUs include acetohexamide, tolbutamide and chlorpropamide. The latter drug has a long duration of action, up to 48 hours, and even its metabolites have active hypoglycaemic potential.

Examples of the second-generation group include glibenclamide (Daonil®), glipizide (Minidiab®), and gliclazide (Diamicron®). Glimepiride (Amaryl®) is classified as a third-generation SU.

All of them have a number of generics available, and most of the generics are of equal potency. All of them stimulate insulin release from pancreatic ß-cells that have residual function. They display, to some extent, a glucose-dependent effect, but still have a potential for serious hypoglycaemia, which is especially a problem with chlorpropamide, especially in the context of skipped meals. Chlorpropamide use is thus best avoided.

Weight gain of 4–6 kg is the other important side effect.[3]

Most clinical trials have shown a maximum reduction of 20% in plasma glucose concentrations, or a drop in HbA1C of 1.5–2.0 % with SU monotherapy as compared to placebo.[11]

Side effects of SUs are observed in up to 5% of patients. Less commonly sulpha allergies may be experienced. SUs should be started at low doses and titrated up every 1 to 4 weeks up to a maximum effective dose.[2] There is no merit in combining two SUs since they belong to the same class of drugs.

Non-sulphonylurea secretagogues (Meglitinides)

These drugs, the so-called glinides, include repaglinide (NovoNorm®), a benzoic acid derivative, and nateglanide (Starlix®), a phenylalanine derivative. These agents are short-acting insulin secretagogues. Both have a similar action to SUs, acting on the same ß-cell receptors. They act on the ATP dependent potassium channels in pancreatic ß-cells, allowing opening of calcium channels and increased insulin release.

They are differentiated from SUs by their much shorter half-lives, and the absence in them of the sulphonic acid moiety, which allows them to be used where patients are allergic to sulphas. In view of their shorter duration of action, they have been used as 'prandial drugs', taken just before meals. Their rapid clearance reduces the potential for delayed hypoglycaemia.

As a general rule, the glucose lowering effect of sulphonylureas plateaus after half the maximum dose is reached.

Side effects

In general, the SUs and non-SUs have similar side effects. Hypoglycaemia would tend to be more common in SUs with longer duration of action, for example with chlorpropamide rather than with the glinides.

The most common adverse side effect is hypoglycaemia. The UKPDS reported an incidence of 1.2% in the SU-treated group.[13] Hypoglycaemia is predisposed to by high doses, missed meals, excessive alcohol, and a history of renal or hepatic disease.

Weight gain is the other significant side effect, and is usually seen in the context of improved glycaemic control. The average weight gain on a SU is some 2–5 kg.[14] Less common side effects include GI disturbance, photosensitivity, abnormal liver enzymes, flushing (especially with chlorpropamide and alcohol), and chlorpropamide-induced hyponatraemia, especially in patients on concomitant diuretic therapy.[15]

Contraindications

- Insulin-dependent type 1 diabetes or diabetic ketoacidosis
- Hypersensitivity to sulphonamides
- Pregnancy and lactation
- Use with caution in renal or hepatic failure

α-Glucosidase inhibitors

These drugs do not target any specific physiologic defect in diabetes; instead they delay the breakdown and absorption of complex carbohydrates in the small intestine by inhibiting the α-glucosidase enzymes found on the brush border of the intestinal wall. Thus, they slow carbohydrate absorption. The inhibition is a competitive and reversible one, lasting up to the next major meal, therefore requiring dosing prior to each carbohydrate containing meal. In the treatment of Type 2 diabetes these drugs are beneficial in addressing the reduction of the postprandial glucose peaks. Since insulin secretion is unaffected, they have no hypoglycaemic effects. Should hypoglycaemia occur related to another drug, it must be remembered to use glucose rather than a complex carbohydrate, as acarbose would inhibit the rapid breakdown of the complex carbohydrate.

The HbA_{1c} level can be reduced by 0.5–1%, and postprandial glucose levels are decreased by about 2.2–2.8 mmol/L with use of these inhibitors.[16]

Due to GI side effects such as flatulence (41–77%), abdominal discomfort (11–21%) and diarrhoea (28-33%), many patients discontinue use of these drugs.[16] These effects are related to the effect of colonic bacteria on undigested carbohydrates in the lower GI tract. These side effects may be minimised in some by titrating the dose up slowly, starting with 25mg per meal.

Acarbose (Glucobay®), available in South Africa, is contraindicated in patients with irritable bowel disease (because it precipitates diarrhoea); intestinal obstruction, or predisposition to obstruction; cirrhosis of the liver; or renal impairment (serum creatinine > 175 mmol/L).

Table I: Comparative details of SUs and non-SUs

Adapted from: Goldstein, Miller et al[12]

Generic Name	Commercial Name	Daily Dose (mg)	Duration of Action (Hr)	Clearance
Sulphonylurea				
1st Generation				
Chlorpropamide	Diabenese®	100–500	> 48	Renal
Tolbutamide	Rastinon®	500–3,000	6–12	Hepatic
2nd Generation				
Glibenclamide	Daonil®	5–15	12–24	Hepatic, renal
Glipizide	Minidiab®	2.5–40	12–18	Hepatic
Gliclazide	Diamicron®	40–160	12–18	Hepatic
3rd Generation				
Glimeparide	Amaryl®	1–8	24	Hepatic, renal
Non-Sulphonylurea				
Repaglinide	NovoNorm®	0.5–16	2–6	Hepatic
Nateglinide	Starlix®	180–360	2–4	Renal

Thiazolidinediones

Thiazolidinediones (TZD) are selective peroxisome proliferator activated receptor (PPAR) gamma agonists. PPARs in humans are associated with gene transcription. Activation of these receptors regulates the transcription of insulin responsive genes involved in the control of production, transport, and use of glucose.

The interactions of TZD result in an

- Increased insulin-stimulated glucose uptake by peripheral tissues (skeletal muscle and adipose tissues) by improving insulin sensitivity

- Reduced hepatic glucose production
- Decreased lypolysis and
- Enhanced adipocyte differentiation[17]

TZD currently available include pioglitazone (Actos®) and rosiglitazone (Avandia®). They can be prescribed as monotherapy or in combination with metformin or sulphonylureas. Its use with insulin is not recommended due to the excessive weight gain and fluid retention. The weight gain may be mediated through a number of mechanisms:

- It usually involves deposition of fat in the peripheral subcutaneous site with a reduction in visceral fat deposition.[19]
- It could also be due to an increase in plasma volume (i.e. oedema) because of the activation of PPAR receptors in the kidneys.
- The oedema may be due to a decrease in renal excretion of sodium and an increase in sodium and free water retention.

Fluid retention and pedal oedema occurs in 3% to 5% of people taking TZD. This can precipitate congestive heart failure in patients with compromised cardiac function. Rosiglitazone and pioglitazone differ in their effects on lipids:

- Rosiglitazone increases LDL-cholesterol (LDL-C) by 0.34–0.47 mmol/L, has no effect on triglycerides (TG), and increases HDL-cholesterol (HDLC) by 0.05-0.09 mmol/L.
- Pioglitazone has a neutral effect on LDLC, decreases TG by 0.29–0.60 mmol/L, and increases HDL-C by 0.09-0.14 mmol/ L.[23] Both agents may reduce the level of small, dense LDL-cholesterol, which is thought to be the most atherogenic lipoprotein component in people with diabetes and may reduce macrovascular morbidity and mortality.[24-26]

TZD demonstrate equivalent HbA1c lowering potential to sulphonylureas and metformin. Clinical trials have shown HbA_{1c} reductions of 0.3% – 1.6% when using TZD as monotherapy in drug naïve patients. As combination therapy with sulphonylureas and metformin the reductions are synergistic and sustained. The A Diabetes Outcome Progression Trial (ADOPT), a large, international, multicentre trial evaluated the efficacy of rosiglitazone monotherapy on glycaemic control and progression of diabetes-associated abnormalities in treatment naïve type 2 diabetics.[18] Results of the study demonstrated a reduced risk of monotherapy failure in these patients at 5 years by 32% compared with metformin, and by 63% compared with glyburide (glibenclamide). Rosiglitazone was shown to significantly improve insulin sensitivity and reduce the rate of loss of ß-cell function versus the other two agents.

Other adverse effects that may be expected when using the TZD include upper respiratory tract infections (16%) and headaches (7,1%). Dilutional anaemia (decreased haemoglobin of about 1 g/dL) may also occur due to an increase in plasma volume.[20]

There is an increased incidence of distal extremity fractures reported in postmenopausal women.[21]

TZD are safe with regard to causing liver toxicity. Pioglitazone and rosiglitazone have been associated with an increase in aspartate aminotransferase and alanine aminotransferase greater than 3 times the upper limit of normal at an incidence similar to placebo (0.25%). If the enzyme levels increase to more than three times the upper limit of normal, TZD therapy should be discontinued.[22] They should be used with caution in patients with already established liver diseases.

They should be used with caution in patients with New York Heart Association (NYHA) classification 1 and 2, and are contraindicated in those with NYHA classification 3 and 4. Also use with caution in patients with peripheral oedema as it may worsen with their use.[20]

A recent meta-analysis (N Engl J Med 2007; 356:2457) found that rosiglitazone increased the risk of cardiovascular death (CVD) by 64% and myocardial infarction by 43%. However, the authors acknowledged numerous limitations. In a re-analysis addressing concerns about the methodology, the increased risk in rosiglitazone-associated CVD (17-51% across several different analyses) was lower than originally reported, and not statistically significant. Rosiglitazone may increase the risk of CVD or MI, but it seems clear that, based on current data, this conclusion remains uncertain.

Pre-menopausal infertile women, or those with Polycystic Ovarian Syndrome, may experience resumption of ovulation while on TZD and they should be made aware of the possibility of pregnancy. Use of TZD is contraindicated in pregnancy and lactation.[22]

Pioglitazone is initiated at 15 mg orally daily and titrated up every 3 to 4 weeks to a maximum dose of 45 mg. Rosiglitazone's starting dose is 4 mg once daily and is titrated up at the same interval as pioglitazone to a maximum of 8 mg/day. People with known insulin resistance and/or a contraindication to metformin may find TZD of benefit.

Newer therapy in Type 2 diabetes

Glucagon-like peptide-1 based therapy

Dipeptidyl peptidase IV inhibitors

Glucagon-like-peptide-1 (GLP-1) is an insulinotropic hormone secreted by the Lcells of the small intestine. GLP-1 has several important biologic actions including the stimulation of insulin release in a glucose dependent manner. It also delays gastric emptying, suppresses glucagon secretion from pancreatic α-cells, and has a central anorexic activity. The usual dose of sitagliptin is 100 mg once daily orally.

Patients with Type 2 diabetes have been found to display a decrease in GLP-1 levels and an impaired GLP-1 response to a glucose load. Endogenous GLP-1 has a very short half-life of $<$ 1min due to its inactivation by the DPP-IV enzyme. Thus inhibition of the DPP-IV enzyme has led to its use in diabetes management. DPPIV inhibitors can be used as monotherapy or in combination with metformin or a TZD for the treatment of Type 2 diabetes.[27]

DPP-IV inhibitors lower HbA1c by 0.79-0.94% as monotherapy and have an effect on both fasting and postprandial glucose control. They are considered weight neutral when compared to sulphonylureas and TZD.[28]

The common side effects that may be expected with the DPP-IV inhibitors are nasopharyngitis, increased risk of UTI and headaches. Very rare but serious side effects include allergic reactions of angioedema and Stevens Johnson Syndrome. DPP-IV inhibitors are not associated with hypoglycaemia unless combined with a sulphonylurea or insulin.[28]

DPP-4 inhibitors seem to be an excellent alternative monotherapy where metformin intolerance is a problem, or in older patients. Several studies argue in favour of the use of DPP-4 inhibitors in combination with metformin as a promising second line treatment.[33]

Glucagon-like peptide-1 mimetics and analogues

As mentioned earlier, GLP-1 has a very short half-life in vivo. It is thus not practical to use native GLP-1 therapeutically. However, the development of GLP-1 mimetics and GLP-1 analogues provides resistance to the rapid degradation of GLP-1 by DPPIV observed in the body. This allows for its therapeutic use. Unlike the DPP-IV inhibitors, the GLP-1 analogues have to be given by subcutaneous injection once or twice daily. Although the present article deals with oral hypoglycaemic agents, we have included this class of drugs, which need to be given by injection, as newer modalities of therapy.

The GLP-1 analogues show:

- Larger reductions in HbA1c by 0.8-1.7% and a weight loss of 1.75-3.8 kg which is mediated through:
  - Promotion of satiety leading to reduction in food intake.[36]
  - Regulation of the gastric rate of emptying, limiting postprandial glucose excursions.[34,36]
- Furthermore, they increase insulin secretion from the pancreatic ß-cell in a glucose-dependent manner, virtually eliminating the problems of therapy related hypoglycaemia (when used without SUs).
- GLP-1 also suppresses glucagon secretion from the pancreatic α-cells in a glucose-dependent manner, which, in turn, suppresses hepatic glucose output.[34]

Most interruptions or discontinuations of therapy are related to adverse gastro-intestinal events, in particular, nausea.[33]

A long-acting release exenatide formulation (i.e. once weekly), for subcutaneous injection in patients with Type 2 diabetes is being evaluated in clinical trials and shows promising preliminary results.[33]

The long-term effect of GLP-1 based agents on glycaemic control has not yet been established, and their potential impact on ß-cell function in humans remains an area of active investigation, though, in animal models, GLP-1 stimulates ß-cell regeneration and neogenesis.[35]

Further studies are required and will provide better understanding in the use of incretin-based therapy in the treatment of Type 2 diabetes. Their efficacy, safety and cost as compared to older known strategies will be under scrutiny from prescribers and funders alike as newer algorithms are developed for the treatment of Type 2 diabetes. The first of the agents expected to appear on the South African market is exenatide, which currently awaits Medicines Control Council registration.

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