A review of metformin and its place in the diabetes guidelines

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Abstract

Metformin is considered to be the initial drug of choice for type 2 diabetes mellitus, particularly in overweight patients. This is based on its effectiveness in achieving glycaemic control, its favourable effects on weight, its low risk of causing hypoglycaemia and its reasonable cost. More importantly, metformin has also been consistently shown to have a favourable effect on cardiovascular risk factors, and to improve cardiovascular outcomes. It can be combined with other oral hypoglycaemic agents, as well as insulin, allowing for a beneficial additive effect.

This article provides a brief overview on the use of metformin, as recommended by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), in its 2012 guidelines for the management of type 2 diabetes.

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Introduction

Diabetes mellitus is a progressive disease that is characterised by raised blood glucose levels as a result of insulin resistance and pancreatic beta-cell failure.[1] High blood glucose levels affect both small (microvascular) and large (macrovascular) vessels, and result in complications such as retinopathy, nephropathy, neuropathy and cardiovascular disease. The insulin resistance experienced by patients with diabetes is at the core of a cluster of risk factors that are associated with cardiovascular disease. Therefore, effective management of type 2 diabetes aims to achieve glycaemic control, e.g. a target haemoglobin A_{1c} (HbA_{1c}) ≤ 7%), and to address underlying insulin resistance and consequent microvascular and macrovascular complications.

The estimated prevalence of diabetes in adults between the ages of 20 and 79 in South Africa is thought to be 6.5% (approximately three-and-a-half million).[1] However, many more people remain undiagnosed. This can be attributed to the insidious and initially asymptomatic nature of the disease, resulting in patients not seeking early medical attention.[1]

Type 2 diabetes is the most common form of diabetes mellitus, accounting for > 90% of cases. Type 1 diabetes accounts for only 5% of all diabetes mellitus cases.[1,2] Limited local data suggest that more than two thirds of patients with type 2 diabetes in South Africa have a glycosylated HbA_{1c} level above the recommended target of 7%.[1]

In an effort to optimise glycaemic control and to reduce the morbidity associated with diabetic complications, several classes of hypoglycaemic agents have been developed over the years. Biguanides are one of the oldest classes of oral hypoglycaemic agents. Phenformin, buformin and metformin were first discovered in the 1950s. Phenformin and buformin have since been discontinued because of the lactic acidosis that is associated with their use.[3] Therefore, metformin remains the only biguanide that is available for commercial use.

Metformin's mechanism of action

Metformin, e.g. Glucophage®, of which several generic formulations are available, has been well established as the first-line treatment option in the management of type 2 diabetes.

It exerts its effect on blood glucose levels by:

- Inhibiting hepatic glucose production (gluconeogenesis)
- Enhancing glucose uptake by peripheral tissue
- Reducing intestinal glucose absorption, thus leading to reduced postprandial hyperglycaemia.

Collectively, these actions result in a reduction in the glycosylated HbA_{1c} level, the lowering of low-density lipoprotein and an increase in high-density lipoprotein cholesterol.[3]

Place in therapy

Glycosylated HbA_{1c} is the standard measure that is used to determine the level of glycaemic control and guide the approach to therapy. It can be defined as the "weighted" average of blood glucose levels during the preceding 120 days of the erythrocyte's lifespan. The efficacy of metformin, both as monotherapy and in combination therapy in reducing HbA_{1c}, has been documented in a large number of trials. HbA_{1c} reductions of 1.5% have been reported.[4-6]

Pharmacists need to be aware of the correlation between the HbA_{1c}, which is expressed as a percentage, and the estimated average glucose level. A calculator for converting HbA_{1c} into estimated average glucose levels is available from http://professional.diabetes.org/glucosecalculator.aspx[1]

The current SEMDSA guidelines provide recommendations for the management of type 2 diabetes. A summary of these recommendations is provided in Table I below.

Table I: Treatment algorithm for type 2 diabetes[1]

Lifestyle measures	Preferred treatment options
Step 1: Initiate at least one oral medicine at diagnosis	*Metformin (as monotherapy):* To be initiated at the time of diagnosis in patients with type 2 diabetes (normal weight or overweight) unless there are specific contraindications to its use, such as renal impairment.
Step 2: Combine any two medicines	*Metformin plus sulphonylurea:* Although metformin monotherapy is effective in type 2 diabetes, the disease is progressive, and most patients will eventually require additional treatment. If a patient has not reached a goal of HbA_{1c} of < 7% after maximal metformin and lifestyle changes for at least three months, additional therapy may be indicated. It may also be necessary to consider initiating a patient into Step 2 if the HbA_{1c} > 9%.
Step 3: Combine three medicines	If dual therapy after approximately three months fails to meet glycaemic goals, a third agent may be added, e.g. metformin plus sulphonylurea plus basal insulin, or metformin plus a pre-mix insulin.
Step 4: Advanced therapeutic options	Refer to specialist for basal-bolus insulin plus additional therapies, e.g. insulin ± metformin ± acarbose (e.g. Glucobay®) ± incretins (e.g. DPP-4 inhibitors and GLP-1 agonists)

DPP-4: dipeptidyl peptidase-4 , GLP-1: glucagon-like peptide 1

The choice of which agents to add to metformin depends on factors such as the risk of hypoglycaemia, the degree of hyperglycaemia experienced, co-morbidities that the patient may have, the adverse events profile of the medicines, e.g. the risk of weight gain, and the cost of the medication.

Dosing information

The minimum effective dose for metformin is 500 mg/day, with an optimum dose of 2 000 mg/day (1 g twice a day). The maximum dose should not exceed 2 550 mg/day in divided doses.[1,3,5] Treatment should be initiated with the lowest possible dose, and slowly titrated over time until the optimal dose of glucose control is achieved. It can be prescribed as 500 mg or 850 mg tablets, and is available as a regular tablet formulation, e.g. Glucophage®, and as an extended-release formulation, e.g. Glucophag® XR.

The safety of metformin

Metformin causes negligible hypoglycaemia as monotherapy. It has also been reported to be weight neutral as monotherapy, and to promote less weight gain when combined with other antihyperglycaemic agents, including insulin.[1] The most commonly reported adverse effects with the use of metformin are gastrointestinal effects.

Gastrointestinal effects

Gastrointestinal effects that have been reported with metformin include diarrhoea, cramping, bloating and flatulence. These are often transient, and can be minimised by the gradual introduction of the medicine and a gradual increase in the dose used. The use of extended-release formulations, e.g. Glucophage® XR, may be considered to minimise gastrointestinal adverse effects and to improve patient compliance with treatment.

Lactic acidosis

Lactic acidosis that is associated with metformin is a rare, but serious metabolic complication that can occur as a result of metformin accumulation during treatment. When this occurs, it is fatal in approximately 50% of cases. It has an estimated prevalence of 1-5 cases per 100 000.[1,3-5] Lactic acidosis is characterised by anorexia, nausea and vomiting, an altered level of consciousness, hyperpnoea (increased depth of breathing required to meet the metabolic demand of body tissue, such as during or following exercise, or when the body lacks oxygen), and abdominal pain and thirst.

Table II: Metformin use in renal failure[1]

Estimated glomerular filtration rate	Action
> 60 ml/minute/1.73 m^2	No renal contraindication to metformin. Monitor patients renal function annually
45-60 ml/minute/1.73 m^2	Continue metformin use. Monitor patients with renal function every 3-6 months
30-45 ml/minute/1.73 m^2	Use metformin with caution. Do not exceed 1 000 mg/day. Monitor renal function every month
< 30 ml/minute/1.73 m^2	Do not use metformin

Excess lactic acid is cleared through the kidneys in a patient with normal renal function. However, both metformin and lactic acid are cleared less effectively in a patient with renal impairment, and may result in an accumulation of lactic acid and resultant lactic acidosis. The SEMDSA 2012 guidelines suggest that metformin should not be prescribed in patients with an estimated glomerular filtration rate < 30 ml/minute (Table II).

Conditions that induce hypoxia, such as cases of acute myocardial infarction, acute left ventricular failure or septicaemia, as well as hepatic insufficiency, may limit the body's ability to metabolise lactic acid, thus increasing the risk of developing lactic acidosis in the presence of metformin. Additional risk factors for lactic acidosis include advanced age, chronic pulmonary disease, alcoholism and dehydration. Metformin is not recommended for use in these patients. The risk of lactic acidosis may be significantly decreased by regular monitoring of renal function in patients on metformin, and by the use of the lowest effective dose of the medicine.[1,3-5]

Clinicians should be aware of situations that predispose to dehydration, such as fasting before surgery or contrast radiography. Metformin should be stopped at least 48 hours prior to the procedure in these situations, and not restarted until the patient has fully recovered and is eating and drinking normally.

There is increasing evidence to show that in the absence of tissue hypoxia and/or moderate to severe renal impairment, metformin will not result in lactic acidosis.

In the case of lactic acidosis, the offending medicine should be withdrawn. Ensure that the patient is adequately hydrated and provide circulatory support, as required.

Conclusion

Patient education aimed at encouraging self-management is considered to be the cornerstone of diabetes care. The pharmacist can play an important role by becoming part of a team of healthcare professionals who provides structured education to patients. Any structured education programme for patients should include topics such as a basic knowledge of diabetes; the importance of good comprehensive blood glucose control, use and adherence to prescribed medication; adverse effects, and how these can be managed; nutrition (including weight loss where indicated); exercise and other lifestyle measures; insulin injection techniques; as well as self-monitoring of blood glucose and recognition of complications, and how these should be dealt with.

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