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Where do sulphonylureas fit in the type 2 diabetes guidelines?

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Abstract

Sulphonylureas act by binding to sulphonylurea receptors and stimulating insulin secretion from pancreatic beta cells. This class of oral hypoglycaemic agents is still widely used in the management of type 2 diabetes in patients where lifestyle changes alone are insufficient. Although the older-generation sulphonylureas no longer have a place in therapy, the newer-generation sulphonylureas are a widely recognised choice, either as monotherapy, or in combination with insulin and/or other oral hypoglycaemic agents.

Introduction

The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) published the 2012 SEMDSA Guidelines for the management of type 2 diabetes in order to improve healthcare delivery, and ultimately, the quality of life for patients living with diabetes in South Africa.[1]

According to these guidelines, sulphonylureas remain an integral part of the management of type 2 diabetes. Their effectiveness has been demonstrated in clinical trials, as well as clinical practice, and is evidenced by robust glycaemic control and a reduction in the microvascular and macrovascular complications of diabetes.[1,2] In this article, we explore the most important characteristics of sulphonylureas and their place in therapy in the management of type 2 diabetes.

General considerations

Sulphonylureas have been part of the armamentarium used for the management of type 2 diabetes since the 1950s.[1] They act by increasing insulin release from the beta cells in the pancreas (insulin secretagogues).[2,3] As they enhance insulin secretion, they are most effective in the early stages of type 2 diabetes, when beta-cell function is at its greatest. Therefore, some level of pancreatic beta-cell viability is required for these medicines to be effective.[4-6]

Sulphonylureas are indicated for the management of type 2 diabetes in patients who are not controlled by diet alone. They may be given together with another glucose-lowering agent, such as a biguanide, e.g. metformin, basal insulin, a glucagon-like peptide 1 (GLP-1) agonist or a dipeptidyl peptidase-4 inhibitor (DPP-4).[1]

The sulphonylureas are classified as first-, second- and possibly, third-generation agents. The first generation are the older agents and the second and third generation the newer agents, with an improved safety and tolerability profile.[2-4] First-generation sulphonylureas, such as chlorpropamide, no longer appear to have a place in therapy.

Table I lists the first- and second-generation sulphonylureas.

Table I: First- and second-generation sulphonylureas

First-generation sulphonylureas	Chlorpropamide (Hypomide®)
Second-generation sulphonylureas	Glibenclamide (Daonil®) Glipizide (Minidiab®) Gliclazide (Diamicron®) Gliclazide MR (modified release) (Diamicron MR®) Glimepiride (Amaryl®)

The potency of the different sulphonylureas can vary. However, they tend to lower glycated haemoglobin levels to approximately the same extent as metformin.[4] Although the different sulphonylureas are equally effective in lowering blood glucose levels, they have differing pharmacokinetic and safety profiles.

Place in therapy

The SEMDSA guidelines recognise the importance of sulphonylureas in the management of patients with type 2 diabetes.

These guidelines clearly state that the following are indications for the use of sulphonylureas:[2]

- *Option 1:* As monotherapy at diagnosis, in persons who are intolerant to metformin, or in normal-weight individuals or those with marked symptoms of hyperglycaemia.
- *Option 2:* As an adjunct to metformin, basal insulin, a GLP-1 agonist, e.g. exenatide or liraglutide, or a DPP-4 inhibitor, e.g. vildagliptin or saxagliptin.
- *Option 3:* As triple therapy with metformin and basal insulin or metformin and an incretin, i.e. a GLP-1 agonist or a DPP-4 inhibitor.
- *Option 4:* In gestational diabetes. If a clinical decision is taken to treat gestational diabetes with a sulphonylurea, glibenclamide is recommended as the sulphonylurea of choice since it does not appear to cross the placenta to any significant degree.[2,7]

It should be noted that the local package insert for glibenclamide states that its safety during pregnancy and lactation has not been established.[8] Also, there is no evidence of the safety or efficacy of the other sulphonylureas in pregnancy and their use during pregnancy is not recommended.

Combination therapy

A decrease in the number of insulin-producing beta cells contributes to the decline in glycaemic control that is seen in patients with type 2 diabetes. The worsening of insulin secretion and insulin resistance is a feature of the condition itself, although there have been suggestions that sulphonylureas may also exhaust beta-cell function.[6,9]

Most patients using sulphonylureas alone eventually require an additional antidiabetic agent in order to maintain glycaemic control.[6] One or more antidiabetic agents with differing, yet complementary, mechanisms of action, are used to optimise glycaemic control in patients in whom a single agent is no longer adequate. The use of combination therapy provides additional glucose-lowering effects. The combination preparation shows a greater blood glucose-lowering effect than that of a single agent. This has been demonstrated in a number of studies and has resulted in the marketing of fixed-combination preparations. The best studied combination to date is that of metformin and glibenclamide. This is available on the South African market as Glucovance®.

The current approach to the use of combination preparations is to introduce the combination therapy early on in the course of treatment, with the aim of preserving beta-cell function, thereby improving long-term outcomes.[6,10]

Safety profile

The most important adverse effects associated with the use of sulphonylureas are hypoglycaemia and weight gain.

Weight gain of ≥ 2 kg has been reported following initiation of treatment with a sulphonylurea. This may be as a result of their ability to increase insulin levels and to utilise glucose.[2-4]

Hypoglycaemic episodes have been reported with all the sulphonylureas. However, some of them are more likely to cause hypoglycaemia than others. Glimepiride and glipizide, for example, are associated with less hypoglycaemia than glibenclamide.[2] The use of glibenclamide is discouraged in the SEMDSA guidelines.[1]

Other factors may contribute to the development of hypoglycaemia. For example, the elderly are at a higher risk of hypoglycaemia, as are those with renal and hepatic impairment. Should a sulphonylurea be used in these groups of patients, modified-release gliclazide may be the preferred choice as it is associated with the lowest incidence of hypoglycaemia.

Most sulphonylureas undergo renal excretion and should be used with caution in patients with renal impairment. The SEMDSA guidelines recommend that glibenclamide should not be prescribed or dispensed without a record of the patient's valid estimated glomerular filtration measurement of > 60 ml/minute/1.73m^2 as measured during the preceding 12 months.[2]

Table II provides a guide on the use of sulphonylureas in patients with renal impairment.

Cardiovascular safety

Clinical trials indicate that raising circulating insulin levels with sulphonylureas or with other intensive insulin therapy decreases cardiovascular risk in patients with type 2 diabetes.[11-13] In addition, tighter glycaemic control has been shown to decrease the microvascular complications of retinopathy and nephropathy, as well as neuropathy.[11]

Table II: Use of sulphonylureas in patients with renal impairment

Sulphonylureas (brand name)	Use in renal impairment
Glibenclamide (Daonil®)	Stop glibenclamide when eGFR is < 60 ml/minute because of an increased risk of hypoglycaemia
Gliclazide (Diamicron®)	Dosage adjustment is required
Gliclazide MR (modified release) (Diamicron MR®)	No dose adjustments are necessary
Glimepiride (Amaryl®)	Dosage adjustment is required
Glipizide (Minidiab®)	Dosage adjustment is required
Chlorpropamide (Hypomide®)	Chlorpropamide should not be used in patients with renal impairment. Its active metabolites can accumulate in patients with a creatinine clearance less than 30 ml/minute

eGFR: estimated glomerular filtration

Conclusion

Oral antidiabetic agents are typically the first-line treatment in type 2 diabetes. Because of the increased number of classes, mechanisms of action and safety profiles of these medicines, it is important for healthcare professionals to gain a broad understanding of each class of oral agents used to optimise diabetes control.

Sulphonylureas remain an important therapeutic class in the management of type 2 diabetes in South Africa.[14] They can be used alone or in combination with other hypoglycaemic agents so as to maintain glycaemic control. One of their main benefits is that they are inexpensive and are available in a number of generic preparations.

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