

Sulfonylureas: A Widely Used Oral Anti-Hyperglycaemic Medication for Type 2 Diabetes Management

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Abstract

Diabetes mellitus (DM) is a fast growing epidemic and a public health concern all over the world due to its increased incidence and its devastating complications. Sulfonylureas (SUs) are oral glucose-lowering agents that are characterized by efficient glycemic control with cardiovascular safety and renal benefits, and use as the second-line drugs for the management of type 2 diabetes (T2D). Although SUs have some side-effects, its glucose-lowering effect is immediate and stimulates the pancreas to release more insulin. It contributes to the development and progression of hypoglycaemia. It is used as an alternative or a complement to Metformin. SUs should be avoided by the elderly weak patients who are at high risk of hypoglycaemia. In this mini review the basic and clinical pharmacology of SUs are described.

Keywords: diabetes, sulfonylureas, hypoglycaemia, weight gain

1. Introduction

At present diabetes mellitus (DM) is a great global health problem due to its alarming increased incidence. It is a chronic metabolic disorder with high levels of blood glucose; and disturbances in carbohydrate, lipid, and protein metabolism (Luminata et al., 2015). The prevalence of type 2 diabetes (T2D) is increasing throughout the world with a high morbidity and mortality with cardiovascular disease and diabetic nephropathy (Kalyani, 2021). The target of diabetes care is to reduce the risk of acute and long-term complications, increase the lifespan, and improve the health-related quality of life of the diabetes patients (Rodríguez-Gutiérrez, 2017). It is expected that the global prevalence of DM from 9.3% (463 million) in 2019 to be about 10.9% (700 million) in 2045, with global spending on diabetes is also expected to grow from \$760 billion in 2019 to \$845 billion in 2045 (Saeedi et al., 2019).

Sulfonylureas (SUs) are potent glucose lowering drugs and have been used since the 1960s for the treatment of T2D. These medications lower blood glucose by stimulating insulin secretion from the pancreatic β -cells of the islets through the closure of the adenosine triphosphate (ATP)-sensitive potassium (KATP) channel. These are the widely used oral anti-hyperglycaemic medications (Hellman & Taljedal, 1975). These can cause severe hypoglycaemia that may progress to loss of consciousness and coma that can be life-threatening, and frequent requires emergency hospitalization (Monami et al., 2007). These may lead to 1–4 kg weight gain, with stabilization at around six months (Davies et al., 2022).

The functioning of SUs can cause β -cell mass in T2D declines over time, so the dose may need to be increased and ultimately treatment with SUs may failure. SUs are generally taken once or twice day with or before a meal. If a dose is missed, should take it as soon as possible. If the missed is remembered near the next dose, should skip the missed dose and must avoid extra medicine to make up for the missed dose (Luminata et al., 2015). In the USA, after Metformin the most commonly used oral hypoglycaemic drug is Glipizide followed by

Glimepiride and then Sitagliptin (Montvida et al., 2018).

2. Literature Review

The literature review is an introductory section of research that highlights the contributions of other scholars in the same field within the existing knowledge (Polit & Hungler, 2013). It deals with a secondary research sources and does not think about future research work (Gibbs, 2008). It helps the new researchers to realize the subject area of research that has been carried out before (Creswell, 2007). André J. Scheen has observed that SUs have long been the only alternative to Metformin or considered as an ideal complementary therapy in case of failure of Metformin monotherapy. But SU has a high risk of hypoglycaemia and weight gain among T2D patients. Therefore, it is mandatory to take into account the risk of hypoglycaemia when SU is considered in mono-therapy for T2D (Scheen, 2021).

Brian Tomlinson and his coworkers have noticed that SUs are the preferred treatment for some types of monogenic diabetes and selection of T2D patients. These are inexpensive and readily available everywhere, and are the most frequently used second-line treatment for T2D worldwide (Tomlinson, 2022). Sanjay Kalra and Yashdeep Gupta have suggested pragmatic guidance to facilitate safe and effective use of SUs. Their study undertakes a balanced assessment of the advantages and limitations of SUs, and compares the use of various SUs in different clinical situations (Kalra & Gupta, 2015). In another paper, Sanjay Kalra and his coauthors have developed practice-based expert group opinion on certain important but less discussed endocrine and metabolic effects of modern SUs and their usage in the management of DM (Kalra et al, 2019).

Confederat Luminita and her coworkers wanted to analyze the presence of physiological, pathological and behavioral risk factors for the development of diabetes and its related complications among patients treated with oral hypoglycaemic sulfonylureas (Luminita et al., 2015). Devajit Mohajan and Haradhan Kumar Mohajan have studied obesity and its related complications, such as diabetes mellitus, eating disorders, various anthropometric indices (Mohajan & Mohajan, 2023a-u).

3. Research Methodology

The research design is a plan of the researchers to develop research area that is reinforced by philosophy, methodology, and method (Tie et al., 2019). It uses scientific methods to explain, predict, and control the observed phenomenon of a researcher (Babbie, 2017). Methodology is the guideline to perform a good research, where scientific methods are followed precisely and efficiently (Kothari, 2008). It is the systematic and theoretical analysis of the methods applied to a field of study (Patel & Patel, 2019). Therefore, research methodology is the specific procedures that are used to identify, select, process, and analyze materials related to the research matters (Schwandt, 2014). It is the science of studying how research is done scientifically (Patel & Patel, 2019). In this study we have presented the historical background of SUs. Then we have discussed the mechanisms of SUs. Finally, we have tried to highlight advances and side-effects of sulfonylureas. We have also unsparingly consulted valuable articles and books of famous authors. To enrich this paper we have managed some research materials from the internet and websites (Mohajan, 2017a, b, 2018, 2020).

4. Objective of the Study

Sulfonylureas are second-line glucose-lowering drugs with high risk of hypoglycaemia. The main objective of this paper is to discuss the use of Sulfonylureas for the treatment of T2D patients. Other trivial objectives of the study are as follows:

to highlight on historical background of SUs,

to show the advantages of SUs, and

to study the side-effects of SUs.

5. Historical Background of Sulfonylureas

Sulfonylureas (SUs) have been used before World War II to combat bacterial infections. These were discovered, by the French chemist Marcel Janbon (1898-1996) and his coworkers in 1942, who were studying sulfonamide antibiotics (p-amino-sulfonamide-isopropyl-thiodiazole; 2254RP). These were used to treat typhoid fever that leads to several deaths rapidly due to hypoglycaemia (Janbon et al., 1942). In August 1946, it is confirmed that sulfa drugs were responsible for the stimulation of insulin secretion by pancreatic islet β -cells (Levine, 1984). In 1956, the first SU, Tolbutamide, was marketed in Germany, and then other first-generation agents, such as Chlorpropamide, Acetohexamide, and Tolazamide were marketed (Webb et al., 2018). Later in 1984 the second-generation agents, such as Glipizide, Glyburide, and Glibenclamide released (Srivastava et al., 2019). French endocrinologist Auguste Loubatières (1912-1977) demonstrated that this hypoglycaemic effect required the presence of pancreas and was explained by stimulation of insulin secretion (Lavabre-Bertranda & Faillieb, 2021).

6. Mechanisms of Sulfonylureas

Sulfonylureas (SUs) are generally well-tolerated, and are well-established drugs for the treatment of T2D patients. These are typically the next class of drugs used when Metformin is unsuitable or insufficient in achieving control. These lower HbA1c values up to 1–2%, and also are affordable and have long-term safety data (NICE, 2015; Mohajan & Mohajan, 2023v, w). These also decrease hepatic insulin clearance that result in increased serum insulin concentrations (Marshall et al., 1970).

Three commonly used sulfonylureas agents are i) first-generation drugs, and ii) second-generation drugs, and iii) third-generation drugs. First-generation agents are short-chain Sulfonylureas and introduced in the 1950s, starting with Tolbutamide, and followed by Acetohexamide, Chlorpropamide, and Tolazamide (Thule & Umpierrez, 2014). Second-generation agents are developed by expanding the radical group substituted on the benzene ring and Glyburide and introduced in 1984, and followed by Glipizide, Gliclazide, Glycypyramide, and Gliquidone (Gerich, 1989). These are more effective and readily penetrate cell membranes than first-generation drugs, feature a greater selective binding capacity, and have fewer side-effects (Campbell, 1998). Third-generation agent is Glimepiride, and it is approved in 1995. Sometimes it is considered as a second-generation drug (Harrower, 2000). It is the most potent Sulfonylurea with a long duration of action and can be given once daily (McGavin et al., 2002).

Commonly prescribed SUs are Gliclazide and Glimepiride; and Gliclazide is available in both standard- and modified- release forms. These are beneficial only for T2D patients for stimulating endogenous release of insulin. These can be safely used with Metformin or Glitazones (Shyangdan et al., 2011). All SUs increase insulin secretion and enhance insulin activity. Doses of SUs are 2.5–5 mg of Glyburide once daily, 80–320 mg of Gliclazide twice daily, 1–8 mg of Glimepiride once daily. SU drugs should ideally be taken 30 minutes before a meal (Monami et al., 2007).

7. Advances of Sulfonylureas

Sulfonylureas help to reduce microvascular complications of diabetes, such as Retinopathy, Neuropathy, and Nephropathy (Prato & Pulizzi, 2006). These are the most frequently used as second-line treatment for T2D in many parts of the world, and are traditionally added after failure of Metformin (Tomlinson, 2022; Mohajan & Mohajan, 2023v-y). The use of SUs as a monotherapy or in combination has been perceived to increase the risk for major hypoglycemic events as compared to other diabetes medications due to most insulin secretagogues (Yu et al., 2018). Various factors, such as efficacy, safety, tolerability, and cost are considered when a physician prescribes SUs for the management of DM (Kalra et al., 2019).

Sulfonylurea is of low cost as well as a large clinical experience and readily available (Scheen, 2021). These are the oldest and most commonly used anti-hyperglycaemic agents for the treatment of T2D. Popularity of Sulfonylureas has increased among diabetes patients due to their safety, efficacy, extra-pancreatic benefits with effects on endocrine and metabolic aspects, and low cost (Kalra et al., 2019). Modern SUs, such as glimepiride possess unique characteristics, such as effective glycemic control, cardiovascular safety and are now at the forefront in precision medicine (Srivastava et al., 2019).

8. Side-Effects of Sulfonylureas

Some side-effects of SUs are hypoglycaemia, unexpected tiredness, weight gain, stomach upset, skin rash and itching, and increased sensitivity to the sun. The primary side-effect is hypoglycaemia, especially in the elderly and those with renal or hepatic impairment, which appears to happen more commonly with Sulfonylureas than with other treatments (Shyangdan et al., 2011). Also the overdose of SU can result in profound and prolonged hypoglycaemia. Chlorpropamide, Glyburide, and the long-acting Glipizide are the most likely to cause prolonged hypoglycaemia (Stahl & Berger, 1999). Also it has a higher risk of cardiovascular events and mortality (Scheen, 2021). The risk of hypoglycaemia increases with age, severity of comorbidity, in people with high cardiovascular risk, and may significantly impaired renal function (Marx et al., 2015). Hypoglycemia is also related to death, cardiovascular events, myocardial infarction, stroke, cognitive impairment, dementia, impaired autonomic function, fall-related fractures, poor quality of life, and increased healthcare costs (Rodríguez-Gutiérrez et al., 2017; Mohajan & Mohajan, 2023m, o).

Sometimes it creates gastrointestinal problems, such as nausea, vomiting, stomach pain, diarrhea, loss of appetite, and constipation. Sometimes allergic reaction may happen, such as a rash, itching, dizziness, and swelling of the face, lips, throat or tongue (Germino, 2011; Sola et al., 2015). If a diabetes patient faces anyone or more complications, such as difficulties in liver, kidney problem, or if severe the medication, SUs should be stopped and also should consult with physician. Sometimes it can increase the risk of hospitalization. Rational use of SUs these side effects can be minimized (Belhatem et al., 2015).

9. Conclusions

Proper use of SUs as second-line monotherapy or third-line therapy in combination with insulin, Metformin or other oral hypoglycaemic agents (OHAs), can be achieved a safe and a fair T2D control environment. SUs are very effective for glucose lowering and have a low cost for the healthcare system. These have evolved over the years, and consider as an important pillar for the treatment of T2D. Every OHA has some side-effects and SUs also have few side-effects and risk factors. Well-known main side-effects of SUs are hypoglycaemia and weight gain, where risk of hypoglycemia may be reduced when used appropriately according to the advice of T2D specialists. Other risk factors of SUs due to severe hypoglycaemia are cardiovascular disease, β -cell dysfunction, and death. When a T2D patient chooses an OHA, s/he must be very careful about glucose-lowering medications in terms of benefits, harms, convenience, and cost.

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