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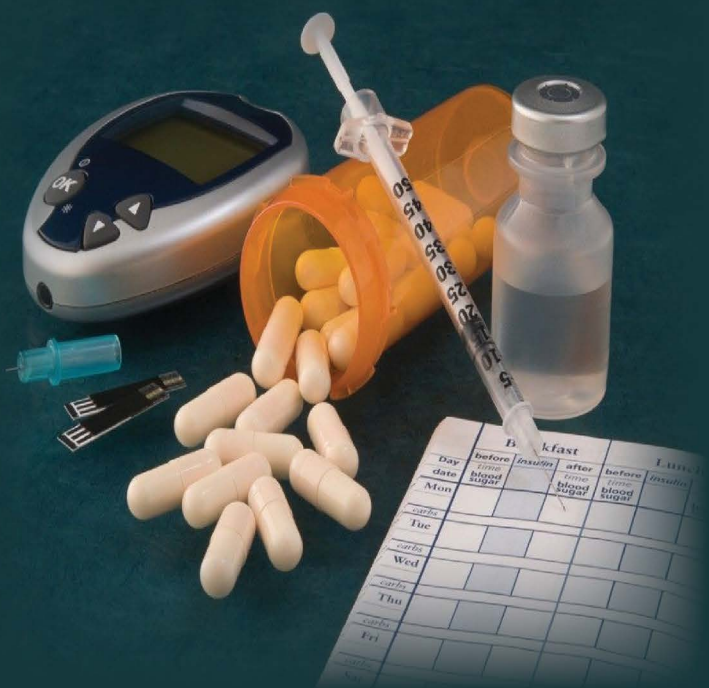
Drugs in Diabetes



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2
CHAPTER

Second-generation Sulfonylureas

Sarita Bajaj, Sanjay Kalra

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INTRODUCTION

The pharmacotherapies available for the treatment of type 2 diabetes mellitus (T2DM) have undergone a dramatic change in the last two decades. Evolution of deeper understanding of the condition at a molecular level and focused research efforts have provided us with newer and more targeted classes of drugs. However, sulfonylureas (SUs) have been used consistently for the past six decades for T2DM treatment, having stood the test of time, considered as contemporary classic in diabetes management. The ancient debate on the safety profile versus the benefits continues to linger on. SUs constitute an important role in the management of diabetes mellitus.

This chapter aims to discuss the historical aspects and the evolution of role of SU as front runners in management of hyperglycemia along with their mechanism of action, safety profile and adverse effects.

HISTORY

It was until 1950s that insulin remained the only pharmacological treatment for type 1 diabetes mellitus (T1DM) and T2DM patients. Then a paradigm shift in the treatment of diabetes was a result of serendipity traced back to 1942 when Marcel Janbon, an infectious disease physician while experimenting with a new sulfonamide for treatment of typhoid fever, shared his findings of post-treatment convulsions, prolonged coma, and significant drop in blood glucose in some of the patients to his physiologist colleague Auguste-Louis Loubatières, who had been conducting diabetes research in dogs during the previous decade. Later Loubatières, after a series of research work, concluded that sulfonamide was an insulin secretagogue acting directly on the pancreas.[1] But it was not until 1956 that the first sulfonylurea, tolbutamide, was introduced commercially in Germany.[2]

TABLE 2.1: Classification of sulfonylureas.

First-generation sulfonylureas	• Tolbutamide • Acetohexamide • Tolazamide • Chlorpropamide
Second-generation sulfonylureas • Conventional • Modern	• Glibenclamide • Glipizide • Glimepiride • Gliclazide • Gliclazide MR, XR • Glipizide XL

(MR: modified release; XR/XL: extended release)

FIRST-GENERATION SULFONYLUREAS

Four drugs, namely, tolbutamide, acetohexamide, tolazamide, and chlorpropamide, were commonly being prescribed by mid-1960s (**Table 2.1**). All these had distinct pharmacokinetics and pharmacodynamics. Nevertheless, the University Group Diabetes Program (UGDP)[3] performed a study over an extended period to observe the efficiency of tolbutamide, phenformin, and insulin. The initial results showed inefficiency and high susceptibility of cardiovascular (CV) mortality with of tolbutamide. As a result, the clinical prescription of these drugs came down substantially and diet modification and/or insulin was considered the treatment of choice.

The successive presentation of errors in UGDP observations and the rejection or disapproval of the results by the American Diabetes Association (ADA), apart from contrasting results obtained by various other researches, generated the establishment of these drugs in clinical use globally. However, the US Food and Drug Administration (USFDA) insists on adding warning insert regarding the increased susceptibility to CV comorbidities in the package of these agents.[4]

SECOND-GENERATION SULFONYLUREAS

Subsequently second-generation SUs, i.e., glipizide, glibenclamide, gliclazide, and glimepiride became available (**Table 2.2**). Glyburide and glipizide were first introduced in Europe for several years before becoming available in the United States in 1984.[4] Glimepiride became the latest second-generation SU to be introduced into clinical practice, first in Sweden and then subsequently got USFDA approval in 1995.[5]

All SUs have been shown to trigger insulin production and probably have the potential to regulate blood glucose in the absence of considerably stimulated production of insulin. This led to the hypothesis that SUs acted on two sites: Firstly, in the β-cell membrane and the next in an unspecified extrapancreatic site. Though it was accepted that SUs reduced blood glucose

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TABLE 2.2: Characteristics of second-generation sulfonylureas (SU).

SU	Daily dose	Duration of action	Dose in renal failure	Dose in hepatic failure	Ischemic preconditioning
Glibenclamide	1.25–20 mg, single or two divided doses	16–24 h	Not recommended in CrCl <50 mL/min	Avoid in severe cases	Abolished
Glimepiride	1–8 mg, single dose	24 h	Reduce, start at 1 mg	Avoid in severe cases	Preserved
Gliclazide	40–320 mg, single or divided doses	10–24 h	No dose adjustment	Avoid in severe cases	Preserved
Gliclazide MR/XR	30–120 mg, single dose	>24 h	No dose adjustment	Avoid in severe cases	Preserved
Glipizide	2.5–40 mg, single or two divided doses	12–24 h	No dose adjustment	Reduce, start at 2.5 mg	Preserved
Glipizide XL	5–20 mg, single dose	>24 h	No dose adjustment	Reduce, start at 2.5 mg	Preserved

(CrCl: creatinine clearance; MR: modified release; XR/XL: extended release)

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level, the mechanism by which this action occurred remained to be elucidated. In 1984, ATP sensitive potassium channel (K_{ATP}) was identified in pancreatic islets. Later in 1995, the precise binding area for SU, Subunit sulfonylurea receptor 1 (SUR1), on the ATP sensitive potassium channel was reported.[6]

Evidence from literature suggests that SUs account for up to 20% of newly initiated oral antidiabetic drugs (OADs), either as monotherapy or in combination, for the treatment of T2DM presumably because they are relatively inexpensive, allow for once-daily oral dosing (in some cases), have reliable efficacy in reducing blood-glucose, and rarely cause symptomatic side effects other than hypoglycemia and weight gain. More than 40 years after the UGDP, their risks versus benefits are still debated.[7] Some SUs are believed to accelerate β-cell apoptosis, increase the risk of ischemic complications, and contribute to nonfatal CV outcomes and all-cause mortality.[8]

However, with the availability of modern second-generation SUs with fewer side effects and better efficacy, their popularity has not waned. A patient centered approach which includes careful selection of SU, the appropriate dosage, proper timing of administration, and adequate patient counseling will ensure that deserving patients are not deprived of the advantages of this well-established class of OADs.[8]

PHARMACOLOGY: MECHANISM OF ACTION

Sulfonylureas are classified as insulin secretagogues (**Fig. 2.1**). They trigger endogenous insulin production by limiting the K_{ATPs} located on pancreatic β-cells. They attach to the SUR subunit located on the β-cell plasma membrane and lead to K_{ATP} channel closing and stop efflux of K^+. Further, the membrane is depolarized thereby allowing influx of Ca^{2+} ions. Finally, this causes stimulation of insulin secretion from secretory vesicles. As production of insulin is a glucose-mediated activity, the regular SUs are analogous with an increased susceptibility of hypoglycemia.[8]

ARE ALL SULFONYLUREAS THE SAME?

Sulfonylureas stimulate insulin secretion by blocking K_{ATP} channels in the pancreatic β-cell membrane by binding to the SUR subunit of the channel. K_{ATP} channels are also present at extra pancreatic tissues, but often contain different types of SUR subunit. Recent evidences suggest that there are variations in the effect of SU on these K_{ATP} channels located in different tissues. For example, tolbutamide and gliclazide block SUR1 with higher affinity as compared to SUR2 while glimepiride and glibenclamide block both SUR1 and SUR2 receptors with similar affinity. The reversibility property shows differences

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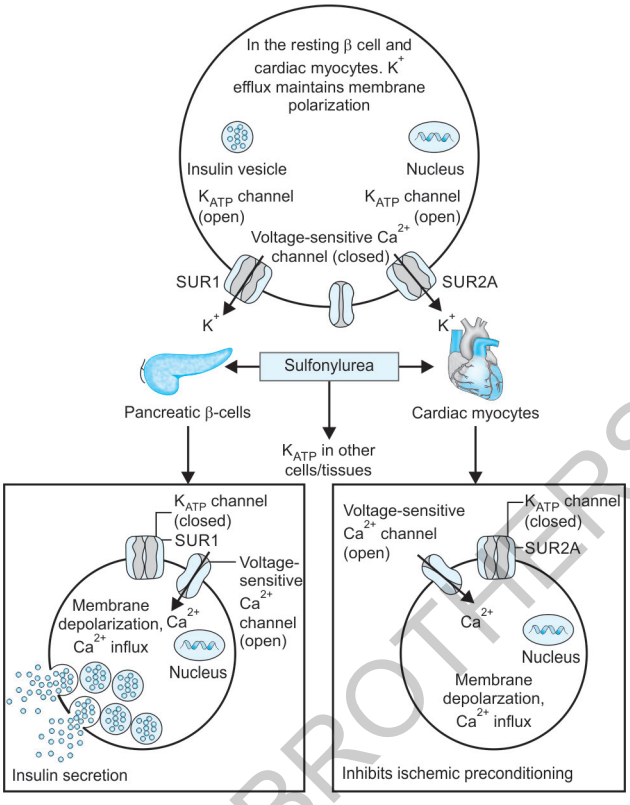

(SUR1: sulfonylurea receptor 1)

FIG. 2.1: Mechanism of action of sulfonylurea.

Source: Adapted from Kalra S, Aamir AH, Raza A, Das AK, Khan AK, Shrestha D, et al. Place of SU in the management of type 2 diabetes mellitus in South Asia: a consensus statement. Indian J Endocr Metab. 2015;19:577-96.

between the agents. On one hand, tolbutamide and gliclazide cause a reversible inhibition of Kir6.2/SUR1 and Kir6.2/SUR2 channels. On the other hand, the cardiac action of glibenclamide is reversible while β-cell, K_{ATP} channels are not reversible. Particularly, SUs that impede SUR1 reversibly (tolbutamide and gliclazide) have lesser number of hydrophobic groups than SUs that are gradually reversible (glibenclamide and glimepiride). The differences can possibly be described by taking into account the hetero-octameric complex of SUR1-K_{ATP} channels that have two high-affinity attachment sites for sulfonyl moiety and benzamido moiety, respectively. The selectivity of SUR1 for the sulfonyl moiety is 100 to 1,000-folds more than that for SUR2. Nearly, all SUs have both sulfonyl and benzamido moieties and interact with SUR1 and SUR2. In contrast, short-chain molecules as in gliclazide attach specifically to sulfonyl site and have no benzamido moiety. This substantiates the selectivity of short-chain SU such as gliclazide by the pancreas partly. Glimepiride triggers insulin production by attaching to precisely 65kD a

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protein site on the K_{ATP} channel of pancreatic β-cell and applies allosteric inhibition of the SUR complex. When contrasted with glibenclamide, glimepiride shows lesser binding affinity (2 to 3-fold) for SUR and more chances of association (2.5 to 3-fold) and dissociation (8 to 9-fold) from the receptor. The specific binding site and receptor associations of glimepiride are supposed to produce lesser inhibition of K_{ATP} channel and therefore the proneness to hypoglycemia is reduced. In addition, the potential of glimepiride to increase both phases of insulin production in T2DM subjects shows a probable association between optimal glycemic control and drastic improvement of regularity of in vivo insulin secretory function. All second-generation SUs except gliclazide are shown to bind to Epac2, a triggering stimulus for insulin exocytosis. As a result, with gliclazide there is lesser susceptibility of hypoglycemia. The changes in pharmacodynamic/pharmacokinetic (PD/PK) profiles of the specific SUs suggest the distinctions in antidiabetic activity, proneness to hypoglycemia, specificities to multiple tissue specific SURs, influence on myocardial ischemic preconditioning, and insulin secretory factors. Taking these factors into consideration it is better to choose from newer second-generation SUs.[8]

GLYCEMIC EFFICACY

Second-generation SUs have shown a robust evidence for glycemic lowering, both as monotherapy and in combination with other OADs. In a recent systemic review and meta-analysis, SU monotherapy was found to reduce glycated hemoglobin (HbA1c) by 1.51% as compared to placebo. HbA1c reduction and improvement in long-term outcome from intensive glycemic control with SU-based therapies that have been established by numerous significant studies including the UKPDS (United Kingdom Prospective Diabetes Study), the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-release Controlled Evaluation), the ADOPT (A Diabetes Outcome Progression Trial), and the VADTFS (Veterans Affairs Diabetes Trial Follow-up Study).[8]

EFFICACY REGARDING MICROVASCULAR AND MACROVASCULAR COMPLICATIONS

The UKPDS[9] and ADVANCE[10] trials showed an improved long-term outcome with sulfonylurea-based intensive therapy. A 10-year follow-up of UKPDS suggested that intensive control with either insulin or SU was associated with relative risk (RR) reductions of 9% in diabetes-related end point, 24% in microvascular disease, and 15% for myocardial infarction and 13% in death from any cause. In the ADVANCE trial, the strategy

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of intensive glucose control targeting HbA1c under 6.5% involving gliclazide (modified release) reduced the average HbA1c value to 6.5 % in a wider range of patients with T2DM and had significantly reduced the incidence of the combined primary outcome of major macrovascular or microvascular events (i.e., 18.1% in the intensive control group vs. 20.0% in the standard control group). The main contributor to the 10% relative reduction in the primary outcome found with intensive control as compared with standard control was a 21% relative reduction in the risk of new or worsening nephropathy. Also, there was significant reduction in major microvascular events (9.4% in intensive control group vs. 10.9% in the standard control group) without any unfavorable CV outcomes. However, no evidence of a reduction in macrovascular events was found. Additionally, a 10% reduction in risk of serious diabetes complications and 30% in macroalbuminuria development was observed in patients in intensive control group. Similarly, in the ADVANCE-ON study,[11] which used intensive target driven multifactorial approach with SU therapy, the reduction in the risk of microvascular complications (specifically end stage renal disease) was observed. On similar lines, 10-year results of VADTFS[12] demonstrated that intensive treatment results in a 17% relative reduction in major CV events compared to standard care, with no difference in mortality.[8]

ADVERSE EFFECTS

Adverse effects, other than hypoglycemia and weight gain, with the use of modern second-generation SUs include symptomatic hyponatremia, alcohol induced flushing or disulfiram-like reaction, cholestatic jaundice, macular erythema, rash, and blood dyscrasias. Conventional SU may be associated with dizziness and headache, hyponatremia, anemia, leukopenia, and thrombocytopenia.[8]

EXTRAPANCREATIC EFFECTS

Sulfonylureas have insulin sensitizing action by elevating the release of glucose transporter type 4 (GLUT4) transporters and reducing resistance of insulin in peripheral tissues. SUs have a CV influence regulated by impeding sarcolemmal and mitochondrial K_{ATP} channels located on cardiac myocytes and K_{ATP} channels situated on vascular smooth muscle cell. The consequence of this action is the damage of ischemic preconditioning (IPC), a cardioprotective phenomenon. Still glimepiride did not harm IPC, though it showed anti-inflammatory and angiogenic activity inT2DM subjects. Also, an antioxidative and provascular influence is seen with glimepiride due to its reduced toxic advanced glycation end

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products (AGEs) and soluble receptor for AGE (sRAGE) and elevated colony stimulating factors.[8]

Gliclazide applies its extrapancreatic actions by strengthening insulin mediated glucose uptake in muscles (+35%) to elevate insulin sensitivity. These influences are in harmony with post-transcriptional function of gliclazide on GLUT4 transporters. It has been observed that gliclazide decreases hepatic glucose secretion and enhances fasting glycemia. The actions of gliclazide include endovascular and antioxidant actions.

- Reducing microthrombosis through partial inhibition of platelet aggregation/adhesion.
- Elevating vascular endothelium fibrinolytic activity.
- Reducing plasma lipid peroxide.
- Increasing erythrocyte superoxide dismutase.[8]

SECOND-GENERATION SULFONYLUREAS: APPLIED ASPECTS

Beta-cell Apoptosis

Concerns are raised by investigators regarding SU-induced β-cell exhaustion, although the data remains largely inconsistent.[13] Exposure of glibenclamide in cultured human islet cell was found to induce apoptosis.[14] The UKPDS and ADOPT trials also implicated glibenclamide for secondary failure in majority of patients after an effective initial response.[8] However, the data from a systemic review of three RCTs presented a contrasting picture with gliclazide showing lower rates of secondary failure of 7.0% as compared to glibenclamide 17.9% ($p < 0.1$) and glipizide 25.6% ($p < 0.005$), respectively. Potential mechanisms suggested for β-cell apoptosis are sustained stimulation of β-cell by SU and increased oxidative stress.[8,15] Additionally findings that antioxidant treatment in animal models of T2DM protect β-cell damage further suggest that oxidative stress also has an important role to play in β-cell apoptosis. A study examining the dose dependent effects of different SU has shown that gliclazide did not significantly stimulate reactive oxygen species production.[15]

Beta-cell Dedifferentiation

Pancreatic β-cells respond to progression of T2DM by increasing production and secretion of insulin and also by increasing β-cell replication to overcome the insulin resistance. However, this adaptation is reversible, as evident from the fact that β-cell function returns after bariatric surgery in T2DM. But if the metabolic stress continues, β-cells succumb to the metabolic overload and dedifferentiation occurs. All together, these changes result in the escalation of the disease

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and eventually to a non-recoverable loss of a functionally mature β-cell mass.[16]

Beta-cell dedifferentiation may account for reduced β-cell mass and insulin secretion in patients with T2DM. An investigation conducted in early T2DM cases to assess the influence of exenatide, sitagliptin, and glimepiride on the secretory potential of β-cell revealed that glimepiride improved the secretion potential; however, exenatide or sitagliptin did not show such effects (functional β-cell mass). Present research data is not favorable with the proposal that SU have detrimental effects on β-cell mass or activity, especially the newer second-generation SU. In contrast, they seem to enhance secretory potential of β-cell if administered in the initial stages of T2DM.[17]

Weight Gain

Sulfonylureas are linked with weight gain which can be explained by their insulinotropic actions, reduction of glycosuria, and increased caloric intake to prevent/treat hypoglycemia. In the UKPDS, patients on SU monotherapy gained more weight compared to those on dietary intervention. However, second-generation SUs cause lesser weight gain as compared to first-generation SU as evident from the UKPDS study in which it was found that in the cohort at 10 years, patients who were assigned chlorpropamide gained 2.6 kg more ($p < 0.001$) while those assigned glibenclamide gained 1.7 kg more ($p < 0.001$) as compared to the conventional treatment.[18,19] Second-generation SUs such as glimepiride, glipizide XL, and gliclazide MR have established weight neutrality during the first year of therapy.[20-22] Several studies have suggested that once daily administration of glimepiride was associated with weight neutralizing or even reducing effect with weight loss up to 3 kg.[23] When compared to glibenclamide, glimepiride was associated with a significantly greater decrease in bodyweight/body mass index (–2.04 ± 3.99 kg vs. –0.58 ± 3.65 kg, $p < 0.001$; –0.71 ± 1.38 kg/m^2 vs.–0.20 ± 1.28 kg/m^2, $p < 0.001$, respectively) while providing equivalent glycemic control.[24] The ADVANCE trial after 5 years of follow-up showed no weight gain in T2DM patients treated with gliclazide MR.[25] In the GUIDE study, over the 27-week period of follow-up, body weight was stable with mean changes from 83.1 to 83.6 kg and 83.7 to 84.3 kg on gliclazide MR and glimepiride, respectively.[22] Choice of SU especially second-generation SU may be relevant in the context of overweight T2DM patients.[26]

Hypoglycemia

Jennings et al. reported that among the patients treated with SUs, up to 20% had symptoms suggestive of hypoglycemia, although in this study episodes were not always corroborated

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by plasma glucose determinations.[27] Hypoglycemia induced by SU treatment requiring assistance occurs in about 1 in every 100 persons per year.[28] A 10-year followup analysis of the UKPDS demonstrated that annual incidence of at least one hypoglycemic event was 17.7% with SU, almost half than those occurring with insulin, i.e., 36.5%.[18]

Individual SUs differ in their hypoglycemic potential owing to the differences in duration of action, time of administration, dose equivalence and potency of hypoglycemic action. Long-acting SUs such as glibenclamide are more likely to cause hypoglycemia.[26] Glimepiride is characterized by long duration of action; fewer hypoglycemic reactions as compared to glibenclamide (105 episodes vs. 150 episodes) were observed in a prospective double bind trial, possibly because of a better modulation of insulin release.[29] Gliclazide treated patients have been shown to experience lower rates of severe hypoglycemia in a recent systemic review and meta-analysis of clinical trials.[30] Previously, the GUIDE study demonstrated significantly lower rates of confirmed hypoglycemia [blood glucose (BG) <3 mmol/L] with gliclazide MR as compared to glimepiride (3.7% vs. 8.9%; p = 0.003). However, there were no episodes of hypoglycemia requiring external assistance in either arms.[22]

Careful phenotyping of the patient, a thorough assessment for all conditions which may result in SU induced hypoglycemia and precise choice of the agent is recommended.

Cardiovascular Safety

The UKPDS established that SUs do not cause macrovascular complications or mortality in T2DM.[18] This advantage continued for about a decade in those who had achieved optimal glycemic control. Identical outcomes had been revealed from 15 well-designed RCTs spanning over an extended period of 72 weeks. ADOPT, ADVANCE and ADVANCE-ON all of which showed no relation between SU therapy and a higher CV risk or mortality.[31-35]

Administration of current second-generation SU, namely, gliclazide MR and glimepiride in T2DM cases are related with reduced susceptibility of all-cause and CV-related mortality in contrast to regular or first-generation SU.[36-38] A latest case–control trial revealed that the possibility of occurrence of coronary artery disease (CAD) raised by 2.4 times (p = 0.004) with glibenclamide and twice (p = 0.099) with glipizide. On the other hand, the risk reduced by 0.3 times (p = 0.385) with glimepiride and 0.4 times (p = 0.192) with gliclazide.[39]

The results of the recent Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) demonstrated no difference in the composite of time to CV death, nonfatal myocardial infarction, or nonfatal stroke between the linagliptin and glimepiride groups.[40,41]

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Ischemic Preconditioning

Glimepiride has been shown to preserve myocardial preconditioning with few CV adverse event in contrast to glibenclamide (p = 0.01 vs. p = 0.34, respectively).[42,43] The outcome of the latest national registry was identical; susceptibility to acute myocardial infarction was considerably lesser in second-generation SU (gliclazide MR, glimepiride) as against glibenclamide (2.7% vs. 7.5%; p = 0.019).[44] With these results, the favorable influence of second-generation SU in maintaining myocardial IPC has been established even though glibenclamide and glimepiride both show affinity toward SUR2 receptor.[5,42] In addition glimepiride has faster and extended period of action, in spite of reduced stimulation of insulin secretion as against glibenclamide.[45,46]

All-cause Mortality

Varying risk of nonfatal CV outcomes and all-cause mortality has been reported by recent retrospective SU studies, indicating the lack of class effect.[8] A meta-analysis evaluating all-cause mortality risk among SU reported the RR of death of different SUs versus glibenclamide to be: 0.65 (95% CI 0.53–0.79) for gliclazide, 0.83 (0.68–1.00) for glimepiride, 0.98 (0.80–1.19) for glipizide, 1.13 (0.90–1.42) for tolbutamide, and 1.34 (0.98–1.86) for chlorpropamide.[37] However, a retrospective study by Pantalone et al. found no significant difference in the overall mortality risk among individual SU (glyburide, glipizide, or glimepiride) in the entire cohort and concluded that choice of SU does not substantially influence over all mortality. However there was evidence of a trend that in those patients with documented CAD, the over-all mortality was reduced in patients taking glimepiride.[47]

A meta-analysis of 14 trials comparing SU versus metformin monotherapy found that SUs do not significantly affect all-cause mortality (RR 0.98; 95% CI 0.61–1.58) or CV mortality (RR 1.47; 95% CI 0.54–4.01) when compared to metformin in T2DM patients. However, SU decreased the risk of nonfatal macrovascular outcomes significantly (RR 0.67; 95% CI 0.48–0.93).[48] Similar results were observed in a Danish nationwide study which demonstrated no significant difference between gliclazide and metformin for all-cause mortality in both sets of patients, i.e., with and without previous myocardial infarction [hazard ratio (HR) 1.05; 95% CI 0.94–1.16 and 0.90 (0.68–1.20), respectively].[49] Studies evaluating the risk of all-cause mortality of metformin SU combination as compared to metformin insulin combination concluded that among patients with T2DM using metformin, the addition of insulin was associated with an increased risk of a composite of nonfatal CV outcomes and all-cause mortality as compared to addition of SU.[50]

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PLACE OF SECOND-GENERATION SULFONYLUREAS IN CURRENT SCENARIO

For the treatment of T2DM, SUs still command an important position in guidelines across the world. Although concerns have been raised regarding safety of these drugs, the modern second-generation SU have been able to allay those fears to rest. In the light of the heterogeneous nature of T2DM, SUs are likely to continue to be a reliable and effective treatment, particularly as combination therapy. With insulin resistance and defects in insulin secretion being the main contributing factors for the development and progression of hyperglycemia, agents that can tackle these main pathogenic mechanisms represent a rational therapeutic approach. In T2DM patients with a predominant defect in insulin secretion, modern second-generation SUs can be a good choice as a frontline treatment. In addition second-generation SUs such as glimepiride, gliclazide, and glipizide are reliable and effective in glucose lowering and therefore continue to be an important option in the armamentarium for the treatment of T2DM.[7]

CONCLUSION

Second-generation SU continue to be an important option in the management of patients with T2DM owing to their well-established glycemic efficacy, safety, tolerability as well as cost-effectiveness. Considering the fact that many of the clinical concerns associated with the use of SU are agent specific and not class specific, a careful choice of specific SU should be considered for beneficial results. With better glycemic efficacy, long-term outcomes and low medication cost, once again, authors wish to emphasize that modern second generation SU remain as first line agents in the treatment of T2DM. Proper patient selection, choice of drug and dose, patient education and empowerment, and physician training will help ensure effective and safe use of this important class of drugs.

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Salient Features

- This monograph is intended to serve as ready reckoner for commonly used medications to treat patients with diabetes mellitus.
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- This monograph is not intended to replace standard Textbooks of Pharmacology. It should be treated as an aid in Pharmacy.
- It is not a toxicology resource. Please refer to standard texts to familiarize with the adverse side effects/overdose and their management.
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