Chapter 87
Clinical Trials to Clinical Practice: Role of Sulfonylureas in Today’s Practice

Brij Mohan Makkar, Deepak Gupta, Ajay Gainda

INTRODUCTION
Sulfonylureas (SUs) have been available for the treatment of type 2 diabetes mellitus (T2DM) patients since 1950s and still occupy a central position in all international guidelines for diabetes management. With improved understanding of pathophysiology of T2DM and introduction of a number of newer oral agents, there is need to critically re-evaluate the effectiveness and safety of SUs, to assess their place in current management of T2DM. Sulfonylureas have the advantage of multiple formulations, low costs, minimal side effects, demonstrated efficacy in controlling hyperglycemia and reducing microvascular complications. However, recently concern has been raised with respect to their possible adverse effects. In addition to documented increase in risk of hypoglycemia, SUs are believed to favor the development β-cell apoptosis and β-cell exhaustion, endothelial dysfunction with increased risk for ischemic complications and possibly an increased mortality risk. This review attempts to analyze the advantages and disadvantages of available SUs with the purpose of providing a critical appraisal of the role of SUs in the modern treatment of T2DM.

BACKGROUND
Sulfonylureas, the oldest noninsulin drug class presently available for the treatment of T2DM, have been the main pharmacologic approach for treatment of T2DM for many decades because of their reliable efficacy in newly diagnosed patients, limited side effects (mainly hypoglycemia) and low cost.

While first generation SUs chlorpropamide and tolbutamide are obsolete, second generation SUs glibenclamide (glyburide), glipizide, gliclazide and glimepiride are still mainstay of pharmacotherapy for managing T2DM in India. Sulfonylureas improve glucose levels by stimulating insulin secretion by pancreatic β-cell, with elevated circulating insulin levels partially overcoming peripheral insulin resistance. They act by binding to the SU receptor subunit of adenose triphosphate-sensitive K⁺ channels (KATP), reducing K⁺ efflux and thereby causing depolarization of cell membrane which in turn leads to calcium influx and increased release of insulin from β-cells (Figure 1). As add on therapy with metformin, SUs treatment has been shown to cause a greater reduction of HbA₁c than thiazolidinedione’s and a similar effect as insulin.3

ISSUES WITH SULFONYLUREA USAGE
Despite a documented efficacy, low cost and decades of clinical experience backing their usage, SUs in recent times have raised some concerns which tend to limit their use in treating T2DM patients. One, despite their remarkable efficacy in controlling glycemia, patients on SU monotherapy experience a progressive loss of glucose control. Secondly, there are documented side effects of weight gain and risk of hypoglycemia. Studies have also shown that there may be increased cardiovascular risk associated with SU usage. We will try to address these issues one by one and finally try to arrive at a conclusion regarding what should be the positioning of SUs in present day scenario.

BETA-CELL EXHAUSTION

Clinical Evidence
Data from United Kingdom Prospective Diabetes Study (UKPDS) clearly showed that after initial improvement in the glycemic control, use of glibenclamide and chlorpropamide was associated with a progressive deterioration of glycemic control.4 Improvement in glycemic control was associated with an initial increase in the homeostasis model assessment β-cell function index that was followed by a progressive and linear reduction.5 This same phenomenon, however, is noted in patients in conventional treatment arm and those taking metformin, a drug that does not increase insulin secretion and also in patients taking insulin (Figure 2). Therefore, failure or worsening of glycemic control may simply be a fundamental feature of T2DM itself resulting from progressive loss of β-cell function, that is not substantially affected by the type of therapy used.

On the contrary, data from A Diabetes Outcome Progression Trial (ADOPT) study clearly showed that SUs provide less durable glycemic control as compared to metformin and rosiglitazone.6

Experimental Evidence
Loss of β-cell mass and function has raised concern regarding the use of SUs for treatment of T2DM. Studies have shown that these agents may induce apoptosis in β-cell lines and rodent islets and also in isolated human islets.7,8 However, repaglinide and nateglinide did not induce β-cell apoptosis especially at low concentrations. On 4-day exposure of the islets to secretagogues, β-cell apoptosis was apparent for all secretagogues.
Studies in isolated human islets cultured in the presence of therapeutic concentrations of glimepiride, glibenclamide, or chlorpropamide have shown that insulin content decreased significantly after culture with all 3 SUs. Insulin responsiveness to glucose was preserved in islets incubated with glimepiride, but not when islets were preincubated with glibenclamide or chlorpropamide. These alterations were reverted by additional 48-hour incubation in drug-free conditions.

In the UKPDS, the loss of β-cell function was not unique for SUs and also occurred at the same rate in other treatment arms, suggesting that other factors had to be at work. The most apparent factor is hyperglycemia per se, as it is concomitantly present. The toxic effect of hyperglycemia on the β-cell is now well documented.

Table 1: Effect of oral hypoglycemics on glucose levels

<table>
<thead>
<tr>
<th>Agent class</th>
<th>Average fall in fasting plasma glucose (mg/dL)</th>
<th>Average fall in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>60–70</td>
<td>3.3–3.9</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>65–75</td>
<td>3.6–4.2</td>
</tr>
<tr>
<td>Biguanide (Metformin)</td>
<td>50–70</td>
<td>2.8–3.9</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>60–80</td>
<td>3.3–4.3</td>
</tr>
<tr>
<td>α-Glucosidase</td>
<td>25–30</td>
<td>1.9–2.2</td>
</tr>
</tbody>
</table>

Incubation of human islets in the presence of 22.2 mmol/L glucose is associated with significant oxidative stress and marked impairment of glucose-stimulated insulin release which can be blocked by concomitant incubation with an antioxidant compound such as glutathione. Thus, agents with a similar antioxidant effect, may have a beneficial action in preventing loss of β-cell. Gliclazide is known to be a general free radical scavenger.

A recent study in mouse MIN6 β-cells showed that gliclazide protected MIN6 cells from the cell death induced by H$_2$O$_2$, whereas glibenclamide had no significant effect (Figure 3). A similar experiment has been replicated in isolated human islets. Incubation of human islets in the presence of therapeutic concentrations of gliclazide was associated with significant reduction in nitrotyrosine content, a marker of apoptosis, while glibenclamide did not show this effect.

**Long-term Efficacy**

The UKPDS illustrates the progressive nature of T2DM with insidious rises in HbA$_1c$ with time as a result of β-cell loss irrespective of the agents used (Figure 2). As the hypoglycemic effect of SUs is secondary to increased insulin secretion, an adequate β-cell mass is needed. Beta-cell exhaustion is a part of the natural history of progression in T2DM which reduces the efficacy of SUs over the course of time. Results from the UKPDS also suggest that the "failure" rate may not be similar in all SUs. Chlorpropamide was noted to have a higher failure rate than glibenclamide. Gliclazide has also been shown to have a lower failure rate than glibenclamide orglipizide. It is important to bear in mind that SUs do not appear to either increase or decrease the underlying rate of β-cell function decline.

**HYPOGLYCEMIA**

Hypoglycemia represents a major clinical concern relating to SU use. Studies indicate that 10–20% patients get symptomatic hypoglycemia, though the incidence of severe hypoglycemia may be much lower. Over the 10-year follow-up period, UKPDS showed that the annual incidence of patients experiencing at least one hypoglycemic event was 11.0%, 17.7% and 36.5% with chlorpropamide, glibenclamide and insulin, respectively. However, major events were seen in only 1.0%, 1.4% and 1.8%, respectively. The relative risk of severe hypoglycemia in the UKPDS is much lower than the 27% observed in intensively treated type 1 diabetic patients reported by the Diabetes Control and Complications Trial (DCCT) despite similar glycemic control (Figure 4).

Nonetheless, severe hypoglycemic episodes are likely to be more protracted and associated with greater mortality when induced by SUs than with insulin. Hypoglycemia in T2DM tends to be more common among specific groups of patients, namely, older individuals and patients treated with polypharmacy. Concomitant use of insulin and SU-potentiating drugs was also associated with an increased risk of hypoglycemia. Long-acting SUs such as chlorpropamide and glyburide are more likely to cause hypoglycemia. The variation in hypoglycemic risk is the likely consequence of differences in duration, timing, dose equivalence and potency of hypoglycemic action of the individual agents. Glimepiride, a newer SU has been shown to cause fewer hypoglycemic reactions compared with glibenclamide (105 vs 150 episodes), possibly because of a better modulation of insulin release, as a function of prevalent plasma glucose concentrations.

More recently, Glucosamine Unum in Die (Once A Day) Efficacy (GUIDE) study comparing gliclazide modified release (MR) 30–120

**Figure 2:** United Kingdom Prospective Diabetes Study 34—progressive loss of glycemic control with all interventions studied.

* Therapy with Gylburide, Chlorpropamide, Metformin or insulin assigned if fasting plasma glucose (FPG) more than 15 mmol/L or symptoms of hyperglycemia.

Overweight patients Cohort, median values.


**Figure 3:** Viability of MIN6 beta-cell exposed to H$_2$O$_2$ in the presence of gliclazide (5 mmol/L) or glibenclamide (5 mmol/L). Similar results were obtained with 1 mmol/L gliclazide or glibenclamide.


**Figure 4:** Relative risk of hypoglycemia in T1DM patients in DCCT compared to T2DM patients in UKPDS.
Therapeutics

mg daily and glimepiride 1–6 mg daily as monotherapy or in combination with their current treatment (metformin or an α-glucosidase inhibitor), showed no hypoglycemia requiring external assistance for similar HbA1c reduction in both groups and irrespective of age.21 Nonetheless, hypoglycemia with a blood glucose level of less than 3 mmol/L occurred significantly less frequently with gliclazide MR (3.7% patients) compared with glimepiride (8.9% patients; P = .003).

The latter findings outline the need for careful phenotyping of the patient, a search for all conditions that may precipitate SU-mediated hypoglycemia and accurate selection of the agent to be used. If all these procedures are followed, the risk–benefit ratio for the use of a SU is not any worse than that of other oral hypoglycemic agents.

BODY WEIGHT GAIN

Improvement in glycemic control is often associated with some degree of weight gain, a collateral effect common to many anti-diabetic treatments including insulin, thiazolidinedione’s, and SUs.3,4 Of the three options, SUs seem to be associated with much less increase in body weight. In the UKPDS, after 10 years of follow-up, the mean body weight change ranged from a minimum of 1.7 kg for glibenclamide to a maximum of 2.6 kg for chlorpropamide.4 In spite of the fact that body weight gain may be seen as an undesirable effect, the change in body weight should nevertheless be considered in a more comprehensive risk-to-benefit ratio. Increase in body weight during the UKPDS occurred together with achievement and maintenance of good glycemic control and significant reduction in all diabetes-related events, microangiopathy and, to some extent, macroangiopathy.4

Glimepiride has been claimed to be at least neutral with respect to body weight and weight reduction has been observed by some authors.23,24 Body weight neutrality has been reported with other SUs, particularly with extended-release gliclazide and gliclazide MR.21,25 Altogether, these findings may suggest that body weight gain in response to SU therapy may have been overemphasized and that more accurate choice of the agent may allow an easier control of body weight, even in overweight T2DM patients.

SELECTIVITY

During the past several years, the potential adverse effect of SUs on myocardial ischemic preconditioning has emerged as an important concern.26 The actual importance of this issue in clinical practice remains unclear, but it has possibly been exaggerated. Sulfonylureas act by binding of KATP channels on β-cells. Different SUs have different cross-reactivity with cardiovascular KATP channels (Figure 1).26 Pharmacologic agents closing these channels oppose ischemic preconditioning and this effect has raised concern of a possible deleterious effect of SU treatment with respect to cardiovascular mortality. In addition to animal experiments, recent human studies also support interference of some SUs on cardiac function under ischemic challenge.27–29 Thus, in response to dipyridamole stress, T2DM patients treated with glibenclamide compared with insulin had much worse myocardial function.30 More recently, Lee and Chou showed that protection by preconditioning occurred in T2DM patients treated with glimepiride, but not when glibenclamide was used.31 This different selectivity confirms previous experimental findings.7,28 A recent study looking at the effects of short-term and long-term treatment with glibenclamide and gliclazide on forearm post-ischemic reactive hyperemia (RH) in type 2 diabetic patients showed that after short-term administration of gliclazide (80 mg) or glibenclamide (5 mg), RH was not influenced.32,33 However, after 4 weeks of treatment, glibenclamide induced a significant (P = .004) reduction in RH. Gliclazide, conversely, did not induce a reduction in RH. Although this difference is most probably based on different SU receptor binding, other mechanisms may contribute to this protective effect.

Studies have also shown that different SU molecules may have different effects. Several studies have shown that gliclazide also possesses hemorheologic properties, reduces platelet reactivity, stimulates endothelial prostacyclin synthesis and increases fibrinolysis, possibly because of reduction in oxidative stress.34,35 The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study of ~11,000 T2DM patients with high-risk of cardiovascular disease (CVD) demonstrated no harm with respect to cardiovascular risk or mortality in patients treated with gliclazide MR in the intensive control arm.41

In a recent nationwide Danish registry-based observational study, Schramm et al. reported most insulin sensitizers (ISs), including glimepiride, glibenclamide, glipizide and tolbutamide, seem to be associated with increased mortality and cardiovascular risk compared with metformin, while gliclazide and repaglinide appear to be associated with a lower risk than other ISs.42

In interpreting these data, it is of key importance to note that the observation of less benefit with most SUs compared with metformin should not be interpreted as causing harm, as metformin has an estimated risk reduction of approximately 40% for major adverse cardiac events and death compared with placebo.43 When comparing outcomes associated with SUs against metformin, hazard ratios of up to 1.7 would suggest treatment effects similar to or better than placebo, especially when considered in the context of favorable effects on microvascular disease risk associated with improved glucose control.44

MORTALITY RISK

Despite the extensive use of SUs, few randomized studies have assessed long-term mortality outcomes related to monotherapy with individual SUs.5,37 The University Group Diabetes Program (UGDP) was possibly the first study to document that tolbutamide was associated with increased total and cardiovascular mortality, causing the premature discontinuation of the tolbutamide arm in the study.37 On the contrary, the initial UKPDS study found no effect of other older SUs, i.e. chlorpropamide and glibenclamide on macrovascular disease complications or mortality. Few observational studies have reported glibenclamide causing increase in overall and cardiovascular mortality when compared with gliclazide and glimepiride,36,39 whereas a recent large observational study comparing glibenclamide with glimepiride did not confirm increased risk.40

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TRANSLATING EVIDENCE INTO CLINICAL PRACTICE

In depth analysis of the vast literature on SUs suggests that SUs are not only efficacious in the management of T2DM, they are also the most potent and the cheapest agents available. The side effects of hypoglycemia and weight gain do not appear to take away all the benefit of significant HbA1c reduction and reduction in the risk of microvascular complications. Also, when used in combination with metformin, as is recommended by most guidelines, weight gain is not a big problem.

Also, by making judicious choice of which SU agent to use, drawbacks of older SUs can be overcome. There is data to suggest
that some of these drugs may provide persistent glycemic control, while limiting the risk of hypoglycemia and weight gain. Once-diaryl SUs such as glimepiride and gliclazide MR may have much less interference with vasculature ensuring neutrality on the endothelial function and no adverse effect on ischemic preconditioning. Hemorheologic effects of gliclazide MR together with an antioxidant action might provide an antiinflammatory advantage.

**RECOMMENDATIONS FROM APEX ORGANIZATIONS**

Findings from major trials of glucose control in patients with T2DM and the approach to the treatment of T2DM have prompted revised treatment algorithms from all major diabetes organizations. However, despite availability of newer molecules, all treatment guidelines still recommend starting with metformin in most patients on diagnosis of T2DM, and SUs are very much part of the choice available for initiation or as second add on agents and are especially preferred where cost of therapy is a consideration.52-47

**CONCLUSION**

Sulfonylureas still occupy a central position in the recommendations of all the guidelines for treatment of T2DM and are likely to continue to be a reliable and effective treatment, particularly as combination therapy. Advancement in the formulation and established non-glucose lowering properties of specific SU agents still provide an opportunity for effective treatment of T2DM. Given the fact that insulin resistance and defective insulin secretion contribute to development and progression of hyperglycemia, in individuals with a prevalent defect in insulin secretion, use of a SU may sound a better choice as a front-line treatment. The use of once-diaryl administration and the choice of SU agents that may not exert further stress on the β-cell and are associated with better properties other than a glucose-lowering effect may then confer specific advantages. Low cost of therapy, a consideration of immense importance in India is another major advantage which may be of help in getting the large population of diabetes in country to improve their glycemic control.

**REFERENCES**