CHAPTER

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Sulfonylureas in the Management of Type II Diabetes Mellitus

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The sulfonylureas are the most frequently prescribed oral hypoglycemic agent along with metformin. Although the management of diabetes was attempted by the "experts" of the Pharaoah of Egypt 3500 years ago and by Shushruta, the modern times efforts began only in the in the early 1900. In the year 1937, hypoglycemic activity of sulfur compounds was noted, and five years later, Michel Janbon noted hypoglycemia while using antibiotic para amino sulfonamide-isopropyl-thiodiaozole. Its secretogogue action was confirmed by Loubatieres in 1946 and tolbutamide was the first SU to be marketed in Germany in 1950[1-2].

MECHANISM OF ACTION

The mechanism of action of SU can be best understood by reviewing the insulin release by the beta cells. Blood glucose levels below 70 mg/dl triggers cascade of events enhancing protein translation and processing. This results in the influx of glucose through glucose transporter (GLUT). The glycolysis cycle is thus initiated with the release of the ATP which in turn suppresses the activity of ATP sensitive K channels. This channel consist of two separate proteins: one is the binding site of OHA sulfonylurea (and also miglitide) and the other is inwardly rectifying K channel protein Kir6.2. Four SUR1 and four Kir6.2 subunit make up the K_{ATP} channel. The binding of sulfonylureas to SUR1 results in closure of the K_{ATP} channel, increased concentration of intracellular K and depolarization of beta cell membrane. Inhibition of K channels induces beta cell membrane depolarization, which opens voltage dependent Ca^{++} channels and stimulates insulin secretion. In short, sulfonylureas stimulate insulin release from pancreatic beta cells in glucose independent manner.

Glibenclamide and glimepiride, which contain both sulfonylurea and nonsulfonylurea moieties and block both SUR1- and SUR2-containing channels, are postulated to interact with both sites on SUR1, but only a single (benzamido-derivative) site on SUR2.

Currently, sulfonylureas are classified as first- and second-generation drugs, although there is no structural or functional basis for this classification. It is known that some sulfonylureas bind with high-affinity to SUR1, but not SUR2, whereas others interact with both types of SUR. It is therefore proposed that the classification of sulfonylureas, meglitinide derivatives, and structurally related compounds be changed to reflect the functional differences among these drugs, and that they be referred to instead as SUR1-specific and non-SUR1-specific.

CLASSIFICATION OF SULFONYLUREA

1st generation	**2nd generation:**
Acetohexamide	Glibenclamide
Carbutemide	Gliburide
Chlorpropamide	Gliclazide
Glyclamide (tolhexamide)	Glipizide
Tolbutamide	**4th Generation**
3rd generationim	JB253
Glimepiride	

4th Generation: This is a newer group which demonstrates sensitive, reversible and repeated manipulation of K_{ATP} channel state and beta cell activity with visible light, yielding optical control over insulin release. They therefore, offer selective targeting of K_{ATP} channels in pancreas and elsewhere. Hence, they are also called as 'photo-switchable' sulfonylureas. It is a light activated drug ,which is activated when exposed to a blue LED stuck to the skin.When the light is turned off the drug is deactivated ,allowing for a very specific control over insulin release and blood sugar level. It can be switched on for a short time when required after a meal as it targets drug activity to where it is needed in the pancreas.[3]

SUR SPECIFIC AND NON-SPECIFIC SULFONYLUREAS

As discussed earlier, SU stimulate insulin secretion by blocking the ATP sensitive potassium channels in the pancreatic beta cells. SU receptors are also present in other tissues besides pancreas. SUR-1 receptors are present in pancreatic beta cells, SUR 2A are present in cardiac muscles and SUR 2B in smooth muscles. The SU might act selectively or non-selectively on these receptors. Gliclazide and tolbutamide blocks the beta cell SUR receptors (SUR 1) only while glibenclamide blocks all the three types of receptors with similar affinity. While the earlier generation SU are only sparingly used, the classification based on the SUR receptors would be more rationale. However, there appears to be no difference in mortality amongst SUR specific and non specific SU. [4]

VARIABILITY IN SULFONYLUREA RESPONSE-PHARMACOGENOMICS

SU have long been recognized as potent hypoglycemic agents capable of inducing hypoglycemia, especially the first generation. However, it has been observed that 10-20% of patients have less than 20 mg/dl reduction of fasting plasma glucose while 50-60% would have more

Table 1: Drug therapy of tye II DM

Lifestyle changes are the foundation of any type 2 diabetes treatment program	
Monotherapy	Start with metformin (MET) *If A_1c target is not achieved after 3 months of monotherapy, proceed to Dual Therapy*
Dual Therapy	MET + SU MET + TZD MET + GLP-1 RA MET + DPP-4 inhibitor MET + SGLT2 inhibitor MET + basal insulin If A_1c target is not achieved after 3 months of dual therapy, proceed to Triple Therapy
Triple Therapy	MET + SU *or* TZD *or* DPP-4 *or* GLP-1 *or* insulin TZD *or* SU *or* DPP-4 *or* GLP-1 *or* insulin GLP-1 *or* SU *or* TZD *or* insulin DPP-4 *or* SU *or* TZD *or* insulin SGLT2 *or* SU *or* DPP-4 *or* TZD *or* insulin Basal insulin + TZD *or* DPP-4 *or* GLP-1 *If A_1c target is not achieved after 3 months of triple therapy and patient (1) is on oral combination, move to injectable; (2) on GLP-1, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1 or mealtime insulin. Refractory patients: consider adding TZD or SGLT2.*
Combination injectable therapy	MET + Basal insulin + mealtime insulin or GLP-1

than 30 mg/dl reduction in the fasting glucose levels, but failed to achieved desired target. Diabetes Outcome Progression Trial (ADOPT) highlighted SU monotherapy failure and the inter-individual variability, it was largely attributed to declining beta cell function, long standing diabetes, high baseline blood sugar levels, high degree of insulin resistance and genetic polymorphism.

The advances in the genetic polymorphism which may contribute to sulfonylurea failure or variability in response may be summarized as-[5]

a. polymorphisms in drug target genes (i.e., ATP-binding cassette, subfamily C, member 8 [ABCC8] and potassium inwardly-rectifying channel, subfamily J, member 11 [KCNJ11]) and diabetes risk genes (e.g., TCF7L2 and insulin receptor substrate [IRS-1]) have been associated with variability in sulfonylurea response in patients with Type 2 diabetes.

b. ABCC8 encodes the regulatory subunit of the sulfonylurea receptor, and the ABCC8 Ser1369Ala polymorphism has been associated with differential response to sulfonylurea therapy in patients with Type 2 diabetes.

c. KCNJ11 encodes Kir6.2, the pore subunit of the sulfonylurea receptor, and the KCNJ11 E23K polymorphism is associated with inter-individual variability in sulfonylurea response and adverse effects in patients with Type 2 diabetes.

d. The KCNJ11 E23K and ABCC8 Ser1369Ala polymorphisms are in strong linkage disequilibrium. Recent data suggest that the K23/Ala1369 risk haplotype confers increased sensitivity to gliclazidein vitro. This finding is primarily governed by the effects of the Ala1369 risk allele.

e. TCF7L2 is a transcription factor in the WNT signaling pathway and it is a Type 2 diabetes risk gene. Polymorphisms in TCF7L2 have been associated with differential response to sulfonylurea therapy in patients with Type 2 diabetes.

f. IRS-1 is a signal transduction protein that mediates the metabolic effects of insulin. The IRS-1Gly972Arg polymorphism is associated with an increased risk of Type 2 diabetes and an increased risk of secondary.

PLACE OF SULFONYLUREALS IN THE MANAGEMENT OF TYPE II DIABETES MELLITUS

Algorithm in the management of Type II Diabetes mellitus-ADA/EASD 2016 guidelines (Table 1)

The choice of pharmacotherapy in the management should be based upon the efficacy and experience with the drug, cost, potential side-effects, effect on the weight, co-morbidities, hypoglycemia risk and importantly, patient preferences. It is evident from the ADA/EASD guidelines of 2016 that SU are the preferred add-on drugs with metformin. As per the Indian Council of Medical Research guidelines also, sulfonylureas, alongside metformin, remains the mainstay of treatment of diabetes mellitus.[6] The reason for their acceptance is a wide experience, their efficacy to lower blood sugar levels and HbA_1c, low cost, fewer co-morbidities and large acceptance, especially in the developing countries. The newer generation SU, especially non-sulpher containing have fewer episodes of hypoglycemia and decrease microvascular risks. However, they are associated with

mild to moderate weight gain and may blunt myocardial ischemic preconditioning.[7]

An ideal candidate for starting sulfonylurea in Type II Diabetes mellitus would be one who still exhibit some beta cell function, diagnosed for less than 5 years and are willing to follow life style modification programs.

SULFONYLUREAS IN CHRONIC KIDNEY DISEASE

SU should be discontinued once the GFR falls below 45-60 ml/min. Such patients are at increased risk of hypoglycemia due to accumulation of its metabolites.

SULFONYUREAS AND PANCREATIC 'BETA CELL EXHAUSTION'

Beta-cell exhaustion with the use of SU has been a concern with the use of secretogogues and the concept has largely governed the regimens of diabetes management. However, Nyback-Nakel A et al (2010) demonstrated inconsistent results supporting the concept, emphasizing that the decreased C-peptide levels are not due to long term use of sulfonylureas [8]. ADOPT study also demonstrated similar beta cell function after 5 years in all treatment groups. It is suggested that it is the metabolic hyperstimulation of persistent hyperglycemia (glucotoxicity) that is most damaging to the beta cells, rather than the hyperexcitability and hypersecretion produced by chronic use of sulfonylureas induced K_{ATP}channel closure. However, it is possible that chronic use of SU may induce refractoriness of beta cell responsiveness[9].

EVIDENCES

1. Glimipride maintains myocardial preconditioning while glibenclamide might prevent it[10]. Hence, glimipride is not associated with cardiovascular risk in comparison with the earlier generation sulfonylureas.

2. 3rd generation SU have a lower incidence of hypoglycemia as compared to other lower generation SU[11]. In the UK Prospective Diabetes Study (UKPDS), the rate of severe hypoglycemia was about 0.5% in the SU-treated group. A total of 11% of subjects taking chlorpropamide and 17.7% of people taking glyburide had more than one episode of hypoglycemia per year. Glyburide and chlorpropamide were associated with a severe hypoglycemia rate of 1.4 events and 1.0 events per year, respectively (in the intensively treated group of subjects), as compared with a 1.8 event rate in those taking insulin. In the A Diabetes Outcome Progression Trial (ADOPT), in which glyburide was compared with metformin and rosiglitazone as monotherapy, just under 30% of subjects randomized to SU treatment reported symptoms of minor hypoglycemia during the 5 years of study, yet only 0.6% experienced episodes of severe hypoglycemia. Not all SUs are, however, associated with such high rates of hypoglycemia. Glyburide, which is very less frequently used these days is unequivocally associated with more frequent and severe hypoglycemia than other insulin secretagogues in this class, including glipizide and glimepiride.

3. SU lower HbA_1c significantly but increasing the dose does not result in further lowering of HbA1[12]. This reduction of HbA_1c is superior to DPP4 inhibitors. Addition of TZD has fluctuating effect on HbA_1c levels.

4. There is no significant difference between DPP4 inhibitors and sulfonylureas when either is added to metformin monotherapy. However, there is a significant decrease in risk of hypoglycemia in patients using DPP4 inhibitors alone.[13] However, it is observed that adding a DPP-4 inhibitor to metformin is associated with an increased, earlier requirement for treatment intensification compared to adding a SU or Thiozolindendione. The secondary failure rate of SU is better than DPP4 inhibitors.[14]

5. The calculated mortality risk for metformin associated lactic acidosis and glibenclamide-associated hypoglycaemia showed no significant differences.[15]

6. Amongst other sulfonylureas, gliclazide is associated with better glycemic control, HbA_1c and secondary failure rates.

7. ADVANCE trial included subjected predominantly on SU as compared to ACCORD trial which included other classes of oral hypoglycemic medications. ADVANCE showed a comparatively better renal outcomes.

8. Second generation SU are not associated with increased mortality after myocardial infarction as compared to other OHAs and insulin[16].

DIFFICULTIES AND POINTS TO PONDER[17]

1. SUs have tendency to induce hypoglycemia due to its secretogogue effect. There is inverse correlation between HbA_1c and patient reported hypoglycemia. However, the risk of hypoglycemia is less as compared to insulin and metformin combination. The incidence of hypoglycemia and hypoglycemia associated deaths are comparatively less as compared to insulin. Hypoglycemia caused by these agents appears not only to be dose related, but also correlates inversely with BMI.

2. The rationale for associating SU use with adverse cardiac outcomes is based on the mechanism of action of these drugs—by binding to the SUR1 receptor on pancreatic β-cells and closure of the K_{ATP} channels occurs. This leads to a rise in intracellular calcium, which in turn results in insulin exocytosis. K_{ATP} channels are present in a number of other cells including cardiac myocytes, neurons, and smooth muscle cells. In theory, binding of SU to K_{ATP} channels in cardiomyocytes results in inhibition of the protective impact of ischemic

preconditioning, a phenomenon that causes worse cardiac outcomes following myocardial ischemia or infarction[18].In the UKPDS trial, there was a non-significant 16% decrease in myocardial infarction rates in patients treated intensively with SUs at the end of the study but a significant 15% decrease in events in these subjects when evaluated 10 years after the end of the original study, despite the fact that they continued to take SUs and their metabolic control had been the same as the conventionally treated group within a year of completion of the original study. The ADOPT study failed to show any significant increase in cardiovascular events in the glyburide-treated cohort. Sulfonylureas are not associated with increased risk of all-cause mortality, cardiovascular mortality, myocardial infarction or stroke.

3. Tolbutamide, like glyburide blocks increases in blood flow induced by diazoxide, a vasodilator, whose effects are mediated through the opening of ATP-sensitive potassium channels. Conversely, the sulfonylurea glimepiride did not exhibit this effect; furthermore, unlike glyburide, glimepiride does not block the improvements in chest pain and ST-segment depression that usually occur with a second balloon dilation during coronary artery angioplasty. Glicizide is another example of a sulfonylurea drug that appears to restrict its ATP-sensitive potassium channel activity to the pancreas[19].

4. Weight gain, mainly is a result of their effect to increased insulin levels and thus utilization of glucose and other metabolic fuels. The weight gain is more so with the second generation SU. The incidence of weight gain is maximum with glibenclamide as compared to other agents in the class. It is attributed to reduction of glycosuria and increased calorie intake to prevent hypoglycemia. However, Jil mamza et al (2016) observed a very small reduction in body weight with SU.

5. Headache

6. Hypersensitivity in few individuals

7. Safety not established in pregnancy as it may induce hypoglycemia in fetus and new born.

8. Renal failure-increased risk of hypoglycemia. However 3rd generation SU can be used in these situation.

9. Fenofibrates or gemfibrozil is associated with increased risk of hypoglycemia in patients taking SU, especially glyburide.[20] These classes of drugs are most commonly used in diabetics.

10. Sulfonylureas in vitro potentiate insulin action beyond the binding portion of the receptor—primarily at the level of insulin-stimulated glucose transport which is a pointer towards their extra-pancreatic effects. The effects discussed include insulinase inhibition, regulation of free and bound insulin, inhibition of glucose output by the intact liver, and actions upon lipid, ketone, protein, and carbohydrate metabolism[21].

11. There is a growing interest in SUR-1 specific SUs. There is no evidence to suggest that SUR-1 specific and non specific SUs have differential effect on arterial distensibility, endothelial functions or vascular mechanisms in Type II diabetes mellitus[22].

12. Within class there is no difference in time for intensification with insulin or any third agent, whether it is glimepride, gliclazide or tolbutamide.

EXTRA-PANCREATIC EFFECTS OF SULFONYLUREAS[23]

1. Reduces hepatic insulin clearance
2. Inhibit glucagon secretion
3. Enhances insulin sensitivity in the peripheral tissues

The sulfonylureas are the first oral hypoglycemic agents used, are efficacious both as mono therapy and in combination with a wide variety of agents. ADA/EASD also recommend them as an important add-on to metformin. Besides, they are available at a lower cost which is an important consideration in the management of diabetes. They are safe and the concern regarding their cardiovascular safety is not convincingly proven. Hypoglycemia produced by these agents needs caution, but it is much less with the newer agents.

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