Editorial

Sulfonylureas: Assets in the past, present and future

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The last two decades have seen an unprecedented increase in the number of drugs available for use in diabetes. In the excitement surrounding the birth of "novel" or "modern" medicines, unflattering opinions are often formed regarding older or traditional classes of drugs. The release of each new entity is accompanied by comparisons with previously available molecules. The discussion regarding choice of drug therapy often becomes subjective and conjectural, instead of the unbiased, evidence-based opinion that is needed. Newer classes of drugs also tend to carry with them an aura of being a panacea, as stress is laid on their extra-pancreatic, extra-glycemic, pleiotropic, cardiovascular and composite effects. This tends to detract from the fundamental philosophy of modern diabetes care, which calls for a patient-centerd approach,[1] in which drug therapy is decided according to the patient's needs, and not vice-versa.

One silent spectator to these trends is the class of sulfonylureas (SU). The longest serving class of oral anti-diabetic drugs, the history of SU can be traced back to pre-World War II days, when hypoglycemic effects of sulfonamide antibiotics were noted. Researchers were soon able to develop similar compounds for use in type 2 diabetes. Tolbutamide and chlorpropamide helped countless persons with diabetes achieve good glycemic control, before newer generation SUs like glibenclamide were introduced. These, in turn, have been supplemented by other compounds including second-generation glipizide, gliclazide, and third-generation glimepiride.[2] Another class of secretagogues, viz., repaglinide and nateglinide is also available for use.

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Modern literature, which focuses on the advantages of recently developed drugs, tends to raise doubts about SU efficacy, safety, and tolerability, SUs, however, are used extensively in many part of the world. Though American and European recommendations may criticize SUs[1,3] national guidelines from China, Japan, Korea, and Taiwan, as well as from the International Diabetes Federation clearly favor SU use.[4-8] This editorial explores some relevant facets of clinical pharmacology that may be of help in rational decision making and safe prescription related to SUs.

Concerns

Efficacy and durability

There has never been any doubt about the efficacy of SU therapy.[9] The SUs consistently demonstrate a > 1% reduction in HbA1c. Most modern glucose-lowering molecules are unable to breach the 1% barrier in HbA1c reduction. For societies where the HbA1c at presentation is higher than 8.0%, SU usage seems more rational as compared to that of other OAD classes.

The SUs have documented extra-pancreatic effects, too. Gliclazide demonstrates anti-oxidant effects, both *in vivo* and *in vitro*.[10] Glimepiride not only improves insulin secretion, but also enhances insulin sensitivity.[11] Glimepiride is able to reduce concentrations of inflammatory cytokines while increasing levels of anti-inflammatory cytokines.[12] Significant decreases in the levels of glyceraldehyde-derived advanced glycation end products, (glycer-AGE: Toxic AGE), eotaxin and fibroblast growth factor-2 have been noted with glimepiride therapy. Increases in the levels of granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-CSF, and decreases in the levels of fractalkine, soluble CD40 ligand (sCD40 L), macrophage

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inflammatory protein-β, vascular endothelial growth factor and soluble receptor for AGE are also reported with the molecule.[13] Glimepiride also reduces vascular stiffness in persons with diabetes.[14]

Data from the United Kingdom Prospective Diabetes Study are often interpreted to state that SUs do not act for long periods of time. Modern research in fact, proves that glimepiride has a more sustained effect on beta cell function than exenatide or sitagliptin.[15] In the ADOPT study, too, glibenclamide was able to demonstrate efficacy and durability of action almost similar to that of rosiglitazone and metformin. At the end of 6 years therapy, there remained a 0.3% difference in HbA1c in persons treated on glibenclamide as compared to other drugs.[16] This durability of effect may be linked to the improvement in beta-cell function that is noted with other SUs.[15]

Safety and Tolerability

The risk of hypoglycemia is thought to be the major limitation of SU use. Various meta-analyses reveal a higher rate of hypoglycemia with SU. Significantly more patients in the SU arm than in the metformin arm had mild hypoglycemia (relative risk [RR]: 2.95, 95% confidence interval [CI]: 2.13–4.07) and severe hypoglycemia (RR: 5.64, 95% CI: 1.22-26.00) in a Cochrane review of 14 trials (4560 participants).[17] This is to be expected because of their glucose-independent mechanism of action. Large trials, on the other hand, have been able to demonstrate that SUs can be used without risk of hypoglycemia. In the ADVANCE trial, for example, in which subjects were involved, major hypoglycemia was reported to be uncommon.[18]

There is a body of research, dating back to the University Diabetes Group Program (UDGP) study, which feels that SUs are linked with higher cardiovascular (CV) and all-cause mortality.[19] Careful analysis, however reveals that the UDGP study design was full of flaws, and was criticized by peers for its errors.[20] The excess CV mortality also seems to be due to hypoglycemia and not due to SU use *per se*. Compared with metformin in a Cochrane review,[17] SU did not significantly affect all-cause mortality (RR: 0.98, 95% CI: 0.61–1.58) or cardiovascular mortality (RR: 1.47, 95% CI: 0.54–4.01). SU significantly decreased the risk of nonfatal macrovascular outcomes (RR: 0.67, 95% CI: 0.48–0.93). However, the definition of this outcome was not uniform, and more trials are needed to arrive at robust conclusions.[17]

Weight gain is thought to be another major limiting factor of SU use.[17] Hypoglycemia, defensive snacking, and increased appetite are thought to be possible factors that contribute to weight gain. However, no significant weight gain was reported in the SU-treated arm of the ADVANCE trial.[21]

Essentiality and Economy

The SUs are the only class of OADs, apart from metformin, to be included in the World Health Organization list of Essential Medicines (LEM), as well as all national LEMs.[22] South Asia is home to a large population of people with diabetes, this places a huge financial burden upon already-strained economies. Thus, SUs provide a simple means of achieving good glycemic control in the majority of people with type 2 diabetes.

Intra-Class Differences

All SUs are not the same. Each SU has a unique pharmacokinetic and pharmacodynamic profile, with its own mode of excretion. This implies that each molecule in this class should be considered as a separate entity while discussing indications, usage, and relative contraindications. Modern SUs such as glimepiride and gliclazide are safer to use than first generation SUs.

The Solution

An unbiased review of the literature reveals that SUs are effective, potent glucose-lowering drugs, whose potential is not being optimally harnessed. The unnecessarily hyped fear of hypoglycemia, cardiovascular adverse events, and weight gain, often prevents appropriate usage of this class of drugs. This is unfortunate, especially in resource-constrained settings,[23] where the low cost and other benefits of SU therapy outweigh their disadvantages.

Patient selection

Appropriate selection of patients,[24] correct choice of dosage, frequency and timing of administration, and comprehensive medication counseling[25] can allow routine, safe and effective use of these drugs. Persons at risk of hypoglycemia, e.g., those with renal or hepatic impairment and those with hypothyroidism or hypo-adrenalism should not receive potent SUs. Glipizide is the preferred SU in renal impairment, while glibenclamide is safe for use in pregnancy. Persons with stable coronary artery disease may be prescribed SUs that do not abolish ischemic pre conditioning. SUs must be avoided in acute coronary syndromes.

Drug selection

There is a wide range of SUs to choose from. One should choose molecules that are less prone to causing hypoglycemia. Specific indications exist for certain molecules: Glibenclamide is safe to use in pregnancy and lactation, while glipizide is

preferred in renal impairment. Using SUs in the lower, divided dose helps in achieving better glycemic control with less variability and less risk of hypoglycemia.

Patient empowerment

Patient education on hypoglycemia awareness training, management of hypoglycemia, and empowerment, viz. self-adjustment of SU dosage helps in maintaining safety of long-term SU prescriptions. Currently available SU tablets fixed dose combination, which are often scored, help facilitate self-adjustment of dosage[25] in patients who experience symptoms of hypoglycemia, but are unable to visit the health care provider at frequent intervals.

Patient education

Dietary counseling, physical activity counseling, and medication counseling are essential co-prescriptions of SU therapy. A 3 + 3 meal pattern, consisting of three major meals, and three snacks must be followed. Ideally, the gap between two meals should not be more than 3 h. The exercise prescription should contain specific instructions to strictly avoid moderate/vigorous-intensity exercise during the period between SU administration and food intake.[25] The correct timing of administration of SUs, with relation to meals must be explained.

Conclusion

Sulfonylureas are an effective, safe, well tolerated and economical class of drugs, with well-documented history. They are extensively used across the world and are recommended by various professional bodies. Appropriate patient selection, drug and dosage selection, and patient education and empowerment, can ensure safe glycemic control with SUs. Apart from patient education, physician education is equally necessary to ensure safe usage of these drugs. SUs are an asset for diabetes care and should be viewed as such.

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