Sulfonylureas

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Abstract

This review describes the basic and clinical pharmacology of sulfonylureas. It undertakes a balanced assessment of the advantages and limitations of sulfonylureas, and compares the use of various sulfonylureas in different clinical situations. The authors suggest pragmatic guidance to facilitate safe and effective use of this class of drugs, and thus help make maximal use of this economical therapeutic option in resource challenged settings such as developed nations.

Keywords: Diabetes, Oral antidiabetic drugs, Glimepiride, Gliclazide, Glipizide, Glibenclamide.

Introduction

Sulfonylureas (SU) have long been established in the treatment of diabetes and were the first oral glucose-lowering medications to be introduced into clinical practice. They account for around 20% of newly initiated oral diabetes medications.[1] They are the mainstay of oral diabetes therapy in many parts of the world, including South Asia, either as first line agents or in combination with other agents.[1,2] They have helped provide symptomatic relief, better quality of life, and euglycaemia, to countless millions of people over the past half century. Their economical cost, availability as fixed dose combinations with metformin, and comfortable acceptance by patients with diabetes, and physicians, alike implies that they cannot be 'whisked away'[2]

One or the other SU has been included in the list of essential oral anti-diabetic drugs by World Health Organization and all countries. Therefore, it becomes imperative to promote rational use of these drugs, to ensure safety, tolerability and efficacy in glucose control. If physicians are aware of the advantages as well as limitations of this class of drugs, they will be able to use them in a more efficient manner. This brief communication hopes to help achieve this goal.

Mechanism of Action

SUs have a glucose independent mechanism of action, which means that they continue to exert their effects irrespective of ambient glucose concentrations in the circulation. They induce insulin release from beta cells by inhibiting ATP-dependent potassium channels. Besides pancreatic beta cells, these channels are present in various tissues of the body including cardiomyocytes and vascular smooth muscle cells (SUR2 isoform). Modern SU such as glimepride act predominantly upon SUR 1 isoforms.

SU also bind with an exchange protein called Epac 2, which interacts with Rap 1 protein to increase the number of insulin vehicles that fuse with beta-cell plasmalemma. This effect has been demonstrated for all SUs except gliclazide.[3]

Pharmacology

Pharmacological properties of various SUs are detailed in Table-1.

Table-1: Pharmacological properties of sulfonylureas.

Drug	Dose	Duration of action	Renal excretion	Biliary excretion
Glibenclamide	1.25-20 mg	12-24 h	50%	50%
Glipizide	2.5-40 mg	12-18 h	80%	20%
Gliclazide	40-320 mg		80-90%	10-20%
Gliclazide MR	30-120 mg	24 h	80-90%	10-20%
Glimepride	1-8 mg	24 h	60%	40%

Efficacy

In a recent meta-analysis of thirty-one double-blinded randomised controlled trials, effect of fixed-dose SU monotherapy or SU added on to other glucose-lowering treatments on HbA1c was studied. SU monotherapy (nine trials) lowered HbA1c by 1.51% more than placebo (95% CI, 1.25, 1.78). SU added to oral diabetes treatment (four trials) lowered HbA1c by 1.62% (95% CI 1.0, 2.24) compared with the other treatment, and SU added to insulin (17 trials) lowered HbA1c by 0.46% (95% CI 0.24, 0.69) and lowered insulin dose. Higher SU doses did not reduce HbA1c more than lower doses.[4]

SU alone or when added to metformin, is associated with the most favourable cost-effectiveness estimate. Treatment with other agents, including

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Table-2: Clinical factors influencing choice of sulfonylurea.

Determinant	Sulfonylurea preferable	Sulfonylurea with caveats	Sulfonylurea not preferable
Age	In younger persons	Low dose in elderly	Glibenclamide not indicated above age 60
Duration of diabetes	In diabetes of lesser duration		In long standing, poorly controlled diabetes
Body weight	In leaner persons	Glimepiride is weight neutral	
Fasting hyperglycaemia	Prefer twice daily dose	Must add metformin; avoid once daily sulfonylurea	
Postprandial hyperglycaemia	Yes	Prefer shorter-acting sulfonylurea	
Comorbid hypertension			Avoid glibenclamide
Comorbid cardiovascular disease		Prefer glimepiride, gliclazide	
Comorbid hepatic or renal dysfunction	No	Prefer shorter acting drug, eg, glipizide	Avoid glibenclamide

Table-3: Pragmatic Use of Sulfonylureas.

- POSOLOGY
  - Begin with low doses
  - Up-titrate slowly, at weekly or fortnightly intervals
  - Avoid using more than half-maximal doses
  - Use more than half-maximal doses only if absolutely essential
- PRESCRIPTION
  - Avoid using sulfonylurea as monotherapy: they should ideally be used if one or two other drug classes fail to achieve glycaemic target
  - Avoid using sulfonylurea at the same time as premixed or rapid-acting insulin
  - Sulfonylurea can be prescribed as part of BIDS (bedtime insulin, daytime sulfonylurea) regime.
  - Avoid using sulfonylurea with other secretagogues (meglinitides)
  - Never use two sulfonylureas together
  - Specify time gap between tablet and meal intake
- HYPOGLYCAEMIA
  - Educate persons with diabetes, and their family members, about hypoglycaemia
  - Enquire about symptoms suggestive of hypoglycaemia at each visit
- LIFESTYLE
  - Advise a 3+3 meal pattern, especially with longer acting sulfonylureas
  - Avoid physical activity during the time interval between sulfonylurea administration and meal intake
  - Avoid missing meals
  - Avoid unaccustomed strenuous physical activity in the first few hours after sulfonylurea ingestion
- WEIGHT
  - Measure weight at each clinic visit
  - Request the person with diabetes to inform in case of sudden, unexplainable weight gain
- CARDIOVASCULAR HEALTH
  - Assess cardiovascular health prior to sulfonylurea prescription
  - Educate persons with diabetes, and family member, about symptoms of angina equivalents
  - Monitor cardiovascular health regularly
- FIXED DOSE COMBINATION(FDCs)
  - Prefer FDCs if available
  - Prefer scored FDCs if available
  - Empower person with diabetes to self-titrate the dose if hypoglycaemia occurs.

thiazolidinediones and dipeptidyl peptidase-4 inhibitors, had unfavourable cost-effectiveness estimates compared with SU, for second line therapy.[1] From a South Asian perspective, however, one must assess the relative costs of drug therapy against the costs of managing potential drug-induced adverse events.

Safety

SU use is thought to be associated with a number of safety issues. Rational use of these molecules, however, can minimize these risks. In the meta-analysis mentioned above, mild-to-moderate hypoglycaemic episodes were significantly more in the sulfonylurea-treated group than in the comparator groups (RR 2.41, 95% CI 1.41, 4.10). None of the trials, however, reported any severe hypoglycaemic events requiring third-party assistance.[4] An increase in weight of 2.31 kg (95% CI 1.31, 3.32) was seen in the sulfonylurea-treated groups compared with comparator groups.[4]

A systematic review and meta-analysis (17 cohort studies, 3 case-control studies including 551,912 T2DM patients overall) which evaluated the all-cause and CV mortality of T2DM patients, found higher mortality among SU users. Patients who received any SU treatment had a higher odds ratio (OR) for all-cause mortality of 1.92 (95% CI = 1.48-2.49) than those who did not receive any SU treatment. When assessing monotherapies only, patients on SU monotherapy had a higher OR for all-cause mortality, 2.48 (95% CI = 1.95-3.16), when compared with any other anti-diabetic monotherapy including insulin (Figure 3), and an OR of 2.63 (95% CI = 2.08-3.04) when specifically compared with metformin.[5]

Patients who received any SU treatment had an overall OR for CV mortality of 2.72 (95% CI= 1.95-3.79) when compared with non-SU patients. Patients on SU monotherapy had an OR for CV mortality of 2.93 (95% CI= 2.16-3.98) when compared with any other anti-diabetic monotherapy including insulin and an OR of 3.09 (95% CI= 2.30-4.14) versus metformin. The validity of these pooled OR estimates is limited by the high level of heterogeneity between the treatment groups of the included studies. The authors of this meta-analysis

themselves mention that higher CV risk demonstrated in patients receiving SU may be independent of SU treatment itself.[5] A Cochrane review which compared Second-generation sulphonylureas versus metformin, thiazolidinediones, insulin, meglitinides or incretin-based interventions showed no statistically significant effects regarding all-cause mortality as well as cardiovascular mortality.[6]

There is conflicting literature on the association between SU and cancer. While a meta-analysis found no evidence that SU was associated with raised cancer risk,[7] another review of 18 studies showed that SU use is associated with an increase in all-cancer risk in cohort studies (RR=1.55 [95% CI=1.48 -1.63]), but not in RCTs (RR=1.17 [95% CI=0.95-1.45]) and case-control studies (OR=1.02 [95% CI=0.93-1.13]).[8]

Pharmacogenomics

Clinical response to these drugs often exhibits significant variation among individuals. Pharmacogenomic evidence so accumulated demonstrates an association between specific gene polymorphisms and inter-individual variability in the therapeutic and adverse reaction effects of sulphonylureas. These polymorphisms are in genes of molecules involved in metabolism, transport and therapeutic mechanisms of the aforementioned drugs. The most common CYP2C9 variant alleles, *2 and *3 lead to impaired metabolism of SU and are associated with reduced oral clearance of SU and increased risk of drug-induced hypoglycaemia. KCNJ11 E23K and ABCC8 S1370A variants in Kir6.2 and SUR1 components of the sulfonylurea receptor affect sulfonylurea therapeutic efficacy and adverse effects. TCF7L2 rs7903146 and rs12255372 gene polymorphisms, which predispose individuals to T2DM development, are associated with diminished therapeutic response to SU.[9]

Use in Specific Situations

There is increased risk of hypoglycaemia with sulfonylureas in patients with renal insufficiency. Glibenclamide should not be used in chronic kidney disease patients beyond stage 2. Glimepiride should be used with caution, beyond stage 2. However, it should not be used in end stage renal disease (ESRD) and patients on dialysis. Safety data regarding use of gliclazide is not available in ESRD and patients on dialysis. Glipizide can safely be used in patients with renal impairment[10] SU can be used in patients with liver disease. However, caution is required in patients with decompensated liver cirrhosis. The preferred SU are those with short half-life such as glipizide. Gliclazide is extensively metabolized in the liver and is contraindicated in severe hepatic insufficiency.[11]

While current guidelines promote the use of glibenclamide in pregnancy, its use should be limited to specific clinical situations where insulin initiation is not at all possible or feasible. The potential adverse effects and lack of long term safety data must be informed to an antenatal patient being prescribed glibenclamide.

Recent Developments in Sulfonylurea Biology

Few authors in recent years have tried to identify factors which determine responsiveness to SU therapy. A recent study from Thailand has demonstrated that decreased basal, but not stimulated, insulin secretion, is a major factor associated with secondary SU failure.[12]

Another study suggests that CYP2C9 gene polymorphism, combined with polymorphism in P450 oxidoreductase (POR* 28allele0), may explain inter-individual variation in sensitivity to SU.[13] Author working on a South Indian population have found that TCF7L2 rs 12243326TT genotype, and KCNJ11 rs 5219TT genotype are associated with higher response rate to SU therapy.[14]

The large ADOPT (A Diabetes Outcome Progression Trial), based on 4360 subjects, treated for a median duration of 4 years, demonstrated a significantly lower risk of serious cardiovascular events with SU (1.8%), but not with metformin (3.2%), as compared to rosiglitazone (3.4%).[15]

Definitive data from a dedicated RCT addressing the CV safety question is lacking. Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA), an ongoing large head-to-head CV outcome trial comparing a SU (glimepiride) with a dipeptidyl peptidase-4 (DPP-4) inhibitor (linagliptin), will provide much needed information related to SU safety.

Conclusion

Recent analysis suggests that the debate against SU may have been unfairly one-sided.[16] Writers of a meta-analysis on SU themselves advise caution in interpreting their results.[17] A biased focus on newer oral hypoglycaemic agents, however, means that readers sometimes get a skewed opinion about diabetes praxis especially related to SU. This brief communication hopes to address this issue.

SU have a definite role to play in diabetes care, not only in South Asia, but across the globe. Pragmatic use of these molecules as second or third line therapy, in combination with metformin, other oral hypoglycaemic agents, and, at times, insulin, can help achieve good glycaemic control, in a safe and well tolerated manner. Tables-2 and 3 presents a few suggestions which will help the reader utilize this class of drugs efficiently.

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