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Treating Diabetes - A Matter of Selectivity of Sulphonylureas

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INTRODUCTION

Diabetes is gaining the status of a potential epidemic in India at a faster rate with more than 62 million individuals currently diagnosed with the disease. According to 2000 statistics, India (31.7 million) topped the world with the highest number of people with diabetes mellitus, followed by China (20.8 million) and United States (17.7 million).

Numerous antidiabetic drugs with different mechanisms are currently available for treatment of type 2 diabetes mellitus (T2DM). Sulphonylureas (SUs) are commonly used in the treatment of T2DM. SUs stimulate insulin secretion by closing ATP sensitive K^+ (K_{ATP}) channels in pancreatic beta-cells by binding to the SU receptor SUR1.

Unlike other SUs, gliclazide, a second generation SU oral hypoglycaemic agent (OHA) used in the treatment of T2DM, is unique in that it is specific for beta-cell K^+ channel and does not activate Epac2 (Figure 1).

EPIDEMIOLOGY OF DIABETES

Incidence of diabetes in India shows patterns that are related to the geographical distribution of diabetes in India. Preliminary results from a large community study conducted by the Indian Council of Medical research (ICMR) revealed that a higher proportion of the population is affected in Maharashtra (9.2 million) and Tamil Nadu (4.8 million) compared to the states of Northern India (Chandigarh 0.12 million, Jharkhand 0.96 million). It is estimated that by the year 2030, diabetes mellitus may afflict up to 79.4 million individuals in India, 42.3 million in China and 30.3 million in the United States.

EXISTING TREATMENT OPTIONS

T2DM is a major health problem that requires multiple pharmacotherapy. The current available glucose-lowering interventions include:

- Metformin
- Sulphonylureas
- Glinides
- α-glucosidase inhibitors
- Thiazolidinediones (TZDs or Glitazones)
- Insulin

PLACE OF SUs AMONGST OTHER AGENTS

SUs, after their introduction in clinical practice in 1950's, have remained the mainstay of pharmacotherapy in the management of T2DM.The South Asian Federation of Endocrine Societies (SAFES) aims to encourage the rational, safe and smart prescription of SUs and recommends appropriate medication counseling by diabetes care professionals in South Asia.

A careful choice of SUs, appropriate dosage, timing of administration and adequate person-centered care, will ensure that deserving patients are not deprived of the advantages of this well-established class of antidiabetic agents. Furthermore, the role of modern SUs in managing patients with

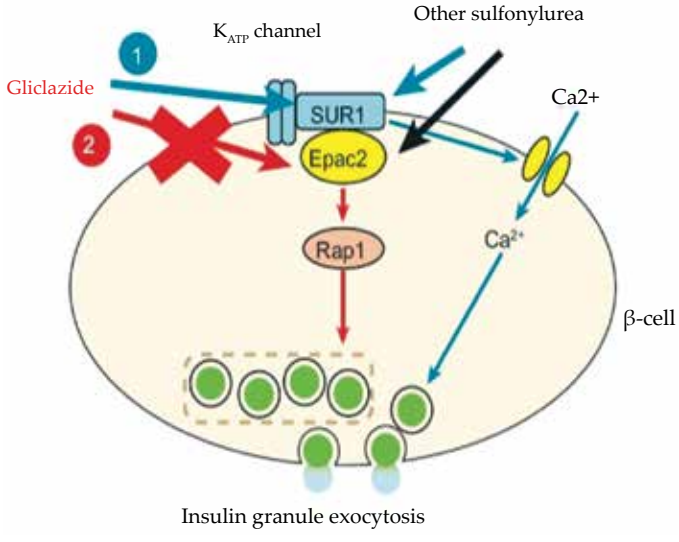

Fig. 1: Mechanism of action of gliclazide on pancreatic beta-cells (SUR: Sulphonylurea receptor; Epac2: Exchange protein directly activated by cAMP 2).

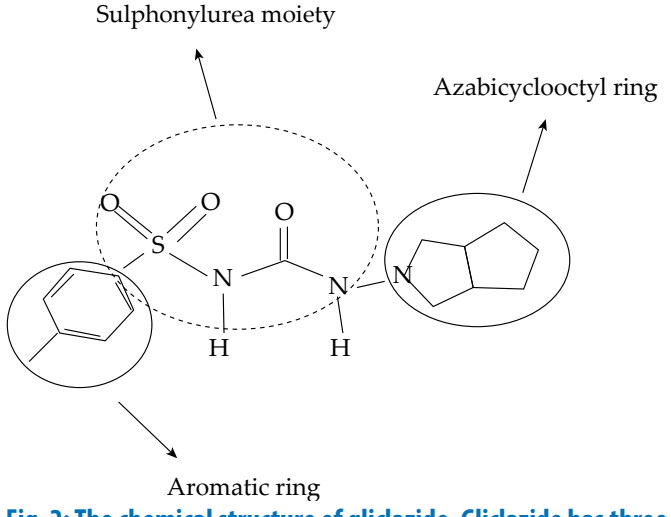

Fig. 2: The chemical structure of gliclazide. Gliclazide has three main structural features, an aromatic ring, a SU group and an aminoazabicyclo-octyl ring.

Table 1: Place of SUs in diabetes therapy

Placement	Approach	Indication
Initial therapy	Monotherapy	Contraindication to metformin Intolerance to metformin
	Combination therapy with metformin	High blood glucose levels at presentation
2nd line therapy	Add on therapy	Inadequate glycemic control with metformin
Subsequent add on therapy	Add on to combination	Inadequate glycemic control with existing oral therapy
Special consideration	Biological factors	Age > 60
		Renal impairment Neonatal diabetes MODY-3
	Psychosocial factors Glucophenotype	Ramadan* Fasting hyperglycemia Postprandial hyperglycemia

*Preferred SUs include modern SUs like glipizide MR, gliclazide, gliclazide MR, glimepiride. MR: Modified release, SUs: Sulfonylureas, MODY: Maturity-onset diabetes of the young.

diabetes is supported by a large body of evidence. Thus, considering their efficacy, safety, pleiotropic benefits and low cost of therapy, SUs should be considered as a drug of choice for the treatment of diabetes in South Asia.

SUs should be preferred as initial therapy in patients with newly or previously diagnosed (<5 years) with functional beta-cell mass, contraindication or intolerance to metformin, high HbA1c levels, suspected Maturity Onset Diabetes of the Young (MODY) and willingness to follow a regular dietary and exercise plan (Table 1).

CLASSIFICATION OF SUS BASED ON SAFES NEW GUIDELINES

Prescription patterns of antidiabetic drugs have changed in recent years with the introduction of newer classes of medications. OHAs still dominate the prescribing pattern in South Asia, either as monotherapy or in combination as majority of the population is treated with OHAs.

As ambiguity exists regarding the most commonly prescribed OHAs, an attempt was made to classify them as conventional and modern SUs based on hierarchy of development and according to duration of action.

CLASSIFICATION OF SULPHONYLUREAS

Hierarchy of development

- Conventional: Tolbutamide, glibenclamide, glipizide
- Modern: Glimepiride, gliclazide modified release (MR), glipizide MR, gliclazide

Duration of action

- Short-acting: Tolbutamide
- Intermediate -acting: Glipizide, gliclazide
- Long-acting: Glibenclamide, glimepiride, gliclazide MR, glipizide MR

SELECTION OF SU BASED ON THE NEED OF THE PATIENTS

For patients with T2DM, a patient-centered approach should be used to guide the choice of pharmacological agents. Efficacy, cost, potential side effects, weight, comorbidities, hypoglycaemia risk and patient preferences should be considered. Few implications for SUs are as follows:

- SUs are an effective, safe, well tolerated, affordable and convenient therapeutic option in the management of T2DM.
- Modern SUs like gliclazide MR and glimepiride should be preferred over conventional SUs in T2DM patients at increased risk of hypoglycaemia.
- SUs with a lower risk of hypoglycemia such as gliclazide MR and glimepiride are recommended in elderly patients.
- Reduction of dose and longer intervals between dose adjustments for SUs are recommended in patients with mild/moderate hepatic impairment.

GLICLAZIDE STRUCTURAL DIFFERENCE

Gliclazide is a powerful free radical scavenger. This unique scavenging effect of gliclazide is due to the aminoazabicyclo-octyl ring that is grafted onto the SU group, which is absent in other SUs (glibenclamide, glimepiride) (Figure 2).

MOLECULAR β-CELL ACTION

It has been found that Gliclazide has intermittent β-cell stimulation rather than a continuous one. Hence the chances of hypoglycemic is much less when compared to other sulphonylureas.

MOLECULAR PERIPHERAL ACTION

Glimipride acts on the peripheral cells having insulin mimetic action Figure 3. The drugs acts on the peripheral cell caveolain the DIG area stimulating the insulin receptor

substrate 1 through non RTK pathway producing the effects of insulin, however it cannot happen in the absence of insulin.

GLICLAZIDE IN HYPOGLYCAEMIA

Hypoglycaemia is the foremost clinical concern when augmenting antidiabetic treatment. Hypoglycaemia induced due to SU with or without the need of external assistance occurs in about 1 in every 100 persons per year. A recent review has shown that patients treated with gliclazide experienced lower rates of severe hypoglycaemia.

The GlUcose control in type 2 diabetes: Diamicron MR vs. glimEpiride (GUIDE) study was the first study to show that gliclazide MR significantly lowers rates of confirmed hypoglycaemia as compared to glimepiride.

Ramadan Trial

Hypoglycaemia is also witnessed frequently in Muslims during the month of Ramadan. In patients with diabetes, fasting can induce hypoglycaemia. According to South Asian guidelines modern SU like gliclazide MR is recommended as effective and economical option during Ramadan. A study in well controlled Asian T2DM patients showed that monotherapy with gliclazide MR in the evening can safely maintain glycaemic control with fewer hypoglycaemic episodes during the Ramadan fast.

BETA-CELL PRESERVATION

Gliclazide have been found to play a role in reducing oxidative stress in T2DM patients by improving plasma antioxidant status. It also has a positive antioxidant effects on beta-cells. Intermittent high levels of glucose leads to increased apoptosis of beta-cells. Gliclazide has been shown to have the unique property to reduce beta-cell apoptosis.

RENAL AND CARDIOPROTIVE PROPERTY OF GLICLAZIDE

Renal Protection

Diabetic nephropathy is the most frequent complication for type 2 diabetic patients, increasing the risk of premature death and affecting the quality of life of the patients. Approximately, 24.9% of patients develop microalbuminuria, 5-20% develop macroalbuminuria, and 20%, a renal functional impairment.

According to Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, patients receiving gliclazide MR showed 21% decrease in new or worsening nephropathy and 30% decrease in macroalbuminuria development.

Cardiovascular Protection

Studies have reported that gliclazide plays a cardioprotective role as it does not interfere with ischaemic preconditioning. ADVANCE trial demonstrated that intensive gliclazide MR treatment led to reduction in cardiovascular death by 12% (Figure 4).

SUs are the mainstream of pharmacotherapy in the management of patients with T2DM. Their glycaemic

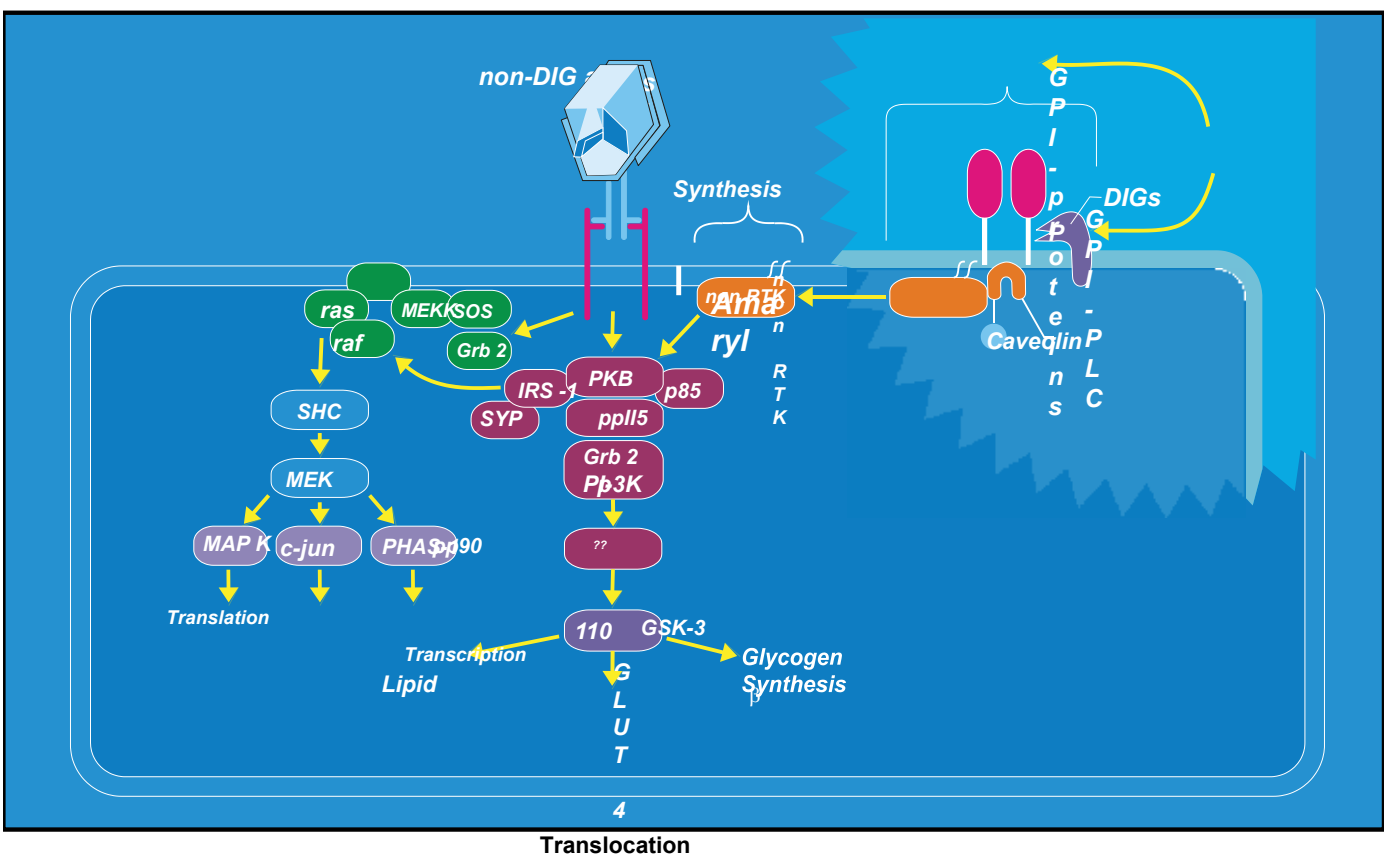

Fig. 3: The metabolic and cardiovascular effects of glimepiride

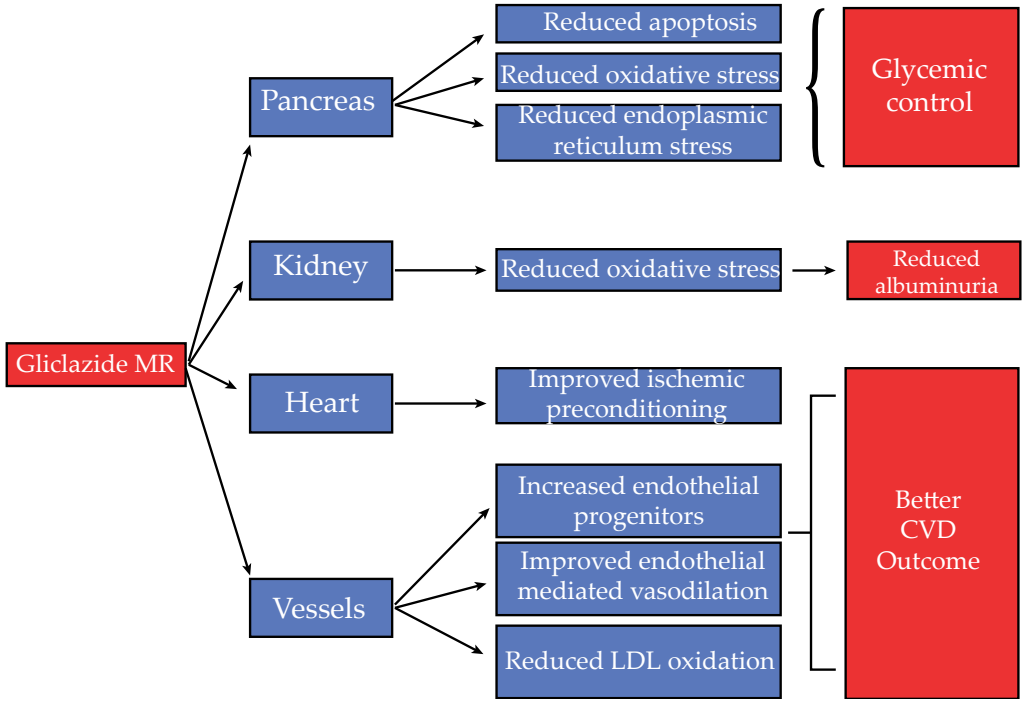

Fig. 4: The metabolic and cardiovascular effects of gliclazide

efficacy, safety and tolerability support make their use as an integral part of diabetes treatment. Considering these factors SUs should be continued to be used as a frontline agent in the treatment of T2DM.

Gliclazide has been found effective in the treatment of the metabolic defects. These actions along with its good general tolerability and low incidence of hypoglycaemia have allowed gliclazide to be well placed within the array of OHAs.

CONCLUSION

This even today a family of drugs discovered more than five decades ago is still alive and available for day to day usage. The developments and discoveries in this family has been the key facts in sustaining this group of drugs. Molecules like gliclazide and Glimipride have been the refined ones and proven beyond doubt that it is useful and safe yet much cheaper for the benefit of the people of countries like ours.

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