Myths and Facts About Glimepiride

M Shunmugavelu[1], Tejas Shah[2], G Vijaya Kumar[3], Jaidev Sudagani[4], Avinash Arivazhahan[5], Jabbar Khader[6], V Mohan[7]

Abstract

Glimepiride is either used as monotherapy or in combination with metformin or insulin for effective control of hyperglycemia in people with type 2 diabetes mellitus. In spite of its effective glucose-lowering potential, similar to other sulfonylureas, glimepiride has been associated with several myths like cardiovascular risk, hypoglycemic effects, weight gain, beta-cell failure, risk in special populations of diabetic patients, and effects of metabolites. Here, we will discuss the myths and facts associated with glimepiride and its safety and concern issues.

Introduction

Sulfonylureas (SUs) are one of the long-standing class of antihyperglycemic drugs. However, in scientific literature, safety, efficacy, and tolerability of SUs are often doubted. Among the widely used SUs in several parts of the world, glimepiride is considered the newest second-generation SUs and is frequently classified as a third-generation SU. The United States Food and Drug Administration has approved glimepiride as the only SU to be used in combination with insulin. Glimepiride is approved as an anti-hyperglycemic drug in more than 60 countries;[1] however, similar to other SUs, several myths prevail regarding the use of glimepiride in the treatment of people with type 2 diabetes mellitus. Here, we will discuss different myths and facts regarding the safety and efficacy of glimepiride in patients with diabetes.

Hypoglycemia

Adverse hypoglycemic effects is the most common myth associated with SUs. It is important to note that glimepiride as a secretagogue differs from conventional SUs primarily because it is associated with lower stimulation of insulin secretion with equivalent metabolic control.[1] Another mechanism responsible for the low rate of hypoglycemia associated with glimepiride is that as compared to conventional SUs, it has two- to threefold lower binding affinity and quick association and dissociation with SU receptor subunits of K_{ATP} channels.[2] In a four-year population-based study to identify severe hypoglycemia in 30,768 patients who attended the emergency division of the region's central hospital, glimepiride was found to induce fewer episodes of hypoglycemia in comparison to the other SU, glibenclamide (6 vs. 38 episodes).[1] Again, a study on pediatric patients revealed that both glimepiride and metformin caused similar rates of hypoglycemia (4.9% and 4.2%, respectively).[2]

Therefore, in contrast to conventional SUs and the myth associated with them regarding severe hypoglycemic effects, glimepiride is a safer SU in this context.

Weight Gain

Weight gain associated with SUs in type 2 diabetes mellitus patients is a common myth, raising concerns over its use in a wide range of people with diabetes. Weight gain is presumed to be one of the major limiting factors of SU use.[3] However, modern SUs like glimepiride as opposed to conventional SUs, have been found to be associated with weight reducing or neutralizing effects. In fact, evidence suggests that in the SU category of antidiabetic drugs, glimepiride is proposed to be associated with least weight gain.[2] Multiple studies have elucidated the 'weight-neutralizing' effects of glimepiride when used as an add-on to metformin therapy.[2] In the CAROLINA trial, after an initial weight gain, there was a decrease in weight in people receiving glimepiride.[4]

Efficacy

Several myths are associated with the efficacy of SUs in controlling hyperglycemic conditions in people with type 2 diabetes mellitus, as compared to other oral antidiabetic drugs.[3] Evidence has demonstrated the efficacy of glimepiride in lowering hyperglycemic conditions in type 2 diabetes mellitus patients, either as monotherapy or as an add-on to metformin or insulin. A study elucidated similar efficacy of metformin and glimepiride in type 2 diabetes mellitus patients.[5] The safety and efficacy of glimepiride/metformin combination in reducing glycemic parameters were found to be better than that of sitagliptin/metformin combination.[6] Glimepiride was found to have sustained glycemic control in patients in the Liraglutide Effect and Action in Diabetes 2 (LEAD-2) trial.[7] A study demonstrated that continuation of glimepiride use in patients on basal-prandial insulin therapy led to sustained benefits in patients with long-term diabetes mellitus.[8] Multiple studies comparing the efficacy of glimepiride/metformin and metformin monotherapy have favored combination therapy over metformin monotherapy. Also, when compared with other oral antidiabetic drugs, such as dipeptidyl peptidase-4 inhibitor (DPP-4i), glimepiride demonstrated better control on hyperglycemic conditions in type 2 diabetes mellitus patients.[2] Taken together, evidence highlights the efficacy of glimepiride in lowering hyperglycemic conditions in type 2 diabetes mellitus patients.

[1]Chairman and Consultant Diabetologist, Trichy Diabetes Speciality Centre (P) Ltd., Tiruchirappalli, Tamil Nadu; [2]Consultant Diabetologist, IVA Diabetes Care Centre Mumbai and S L Raheja Fortis Hospital, Mumbai, Maharashtra; [3]Senior Consultant Diabetologist, Apollo Specialty Hospital and Diabetes Medicare Centre, Chennai, Tamil Nadu; [4]Consultant Endocrinologist, Santhi Endocrine and Diabetes Hospital, Vijayawada, Andhra Pradesh; [5]Medical Affairs, Diabetes and Cardiovascular, Sanofi India Ltd.; [6]Professor and Head, Department of Endocrinology, Government Medical College Trivandrum, Kerala; [7]Chairman and Chief Diabetologist, Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu

Cardiovascular Safety

Another common myth associated with SUs is regarding its safety for use in people with cardiovascular risk. The association with adverse cardiovascular outcomes and increased mortality is the biggest concern with SUs.[7] However as compared to other SUs, glimepiride has been associated with fewer cardiovascular events.[1] As compared to conventional SUs, glimepiride has been found to maintain myocardial ischemic preconditioning with lower cardiovascular adverse effects. Moreover, modern SUs, including glimepiride, do not associate with all-cause or cardiovascular mortality, or increased risk of stroke or myocardial infarction.[9] In the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) trial, glimepiride was found to be noninferior to linagliptin in terms of cardiovascular outcome in type 2 diabetes mellitus patients at high cardiovascular risk. [4]

Ischemic Preconditioning

In contrast to other SUs, ischemic preconditioning of cardiac myocytes is not impaired by glimepiride. There is evidence suggesting that myocardial preconditioning is preserved by glimepiride, which is a protective mechanism to limit damage during an ischemic event. Therefore, compared to other SUs, the use of glimepiride may be safer in cardiac patients since it has been found not to have detrimental effects on cardiac preconditioning.[1]

Beta-Cell Failure

Beta-cell secretagogues, such as SUs are useful for glycemic control in case of patients with type 2 diabetes mellitus since this type of diabetes is characterized by progressive beta-cell failure. Glimepiride stimulates insulin release from pancreatic beta-cells. Glimepiride has been shown to improve both first- and second-phase insulin secretion of beta-cells using euglycemic and hyperglycemic clamp studies.[1] In a study by Gudipaty *et al*, it was found that after six months of treatment, glimepiride appeared to increase beta-cell secretion while no significant effect on functional beta-cell mass was observed in case of exenatide or sitagliptin.[10] Therefore, it is evident from these studies that glimepiride improves beta-cell failure observed in patients with type 2 diabetes mellitus. The long term and sustained efficacy of glimepiride was confirmed recently in the CAROLINA trial as well.[4]

Insulin Secretion Phase Differences

Insulin secretion is biphasic; its plasma concentration increases rapidly at 2–4 min, decreases at 10–15 min, and gradually increases to a pseudo-steady state at 2–3 h. The initial spike is called first-phase insulin release and subsequent increases are referred to as second-phase insulin release. The earliest detectable defect in beta-cell function is reduction in first-phase insulin release,[11] which is a hallmark in the pathogenesis of type 2 diabetes mellitus.[12] While a study reported that glimepiride increases the first-phase insulin release,[12] another study suggested that it increases both first- and second-phase insulin secretion from beta-cells,[13] thereby achieving its control on hyperglycemic conditions in type 2 diabetes mellitus patients.

Use with Basal Insulin

Several older original studies and review papers were not in favour of the use of combination therapy using basal insulin with SU, since SUs might inflict overt stimulation of insulin secretion from beta-cells that might, in turn, accelerate beta-cell death due to apoptosis. However, the majority of experts continue the use of SUs while initiating insulin therapy.[8] A study by Janka *et al*. revealed that more effective glycemic control was achieved in people with type 2 diabetes mellitus poorly controlled on oral therapy by adding basal insulin to glimepiride and metformin, than initiating insulin therapy after discontinuation of the use of oral antidiabetic drugs.[14]

Low Cost of Therapy

It has been revealed in a health economics modelling study and another cost-effectiveness analysis that, in general, the addition of SU drugs like glimepiride to metformin monotherapy is associated with low cost per quality-adjusted life-year gained as compared to other oral antidiabetic drugs, such as dipeptidyl peptidase-4 inhibitors and thiazolidinediones.[7]

Pleiotropy Effects

In addition to its glucose-lowering efficacy, glimepiride has added benefits for patients due to its multiple extrapancreatic pleiotropic effects. It has been found to stimulate lipogenesis and glycogenesis. It has insulin-sensitizing effects as evident from studies on cultured skeletal muscle. In addition, in preclinical studies, it has been found to increase hepatic glucose disposal and reduce insulin resistance.[1] It has potent anti-inflammatory, antioxidative, and angiogenic properties.[15] Because of such additional benefits, apart from effective control of hyperglycemic conditions, glimepiride is a preferred choice of therapy in type 2 diabetes mellitus patients.

Pharmacokinetic (PK) / Pharmacodynamic (PD) Differences from Other SUs

The PK/PD profiles vary for different SUs. The first-generation SUs have more drug interactions, increased incidence of hypoglycemia, and longer half-lives, while the second- and third-generation SUs like glimepiride have lower incidence of hypoglycemia, shorter half-lives and more rapid onset of action.[16] As observed in case of PK profiles, each SU has a unique PD profile, with its own mode of excretion.[3] Glimepiride is metabolized in the liver and its excretion is 60% renal, and its duration of action is 24 h.[2] Therefore, in contrast to few other SUs, both PK and PD profiles of glimepiride are relatively safe for type 2 diabetes mellitus patients.

Metabolite Differences from Other SUs

In general, SUs are mainly excreted either as inactive metabolites or as unexchanged drugs, thereby, producing less hypoglycemia in people with diabetes who have renal impairment. While other SUs, such as glibenclamide can aggravate the risk of hypoglycemia in such patients, glimepiride is reported to be safe in such patients.[2]

Utility in Special Populations

Glimepiride is generally well tolerated in type 2 diabetes mellitus patients. It can also be used in elderly patients. However, its use should be

Table 1: List of common myths and facts regarding glimepiride effects in type 2 diabetes mellitus patients

Myths	Facts
Hypoglycemic effects	Compared to other SUs, glimepiride has been associated with lesser hypoglycemic effects.
Cardiovascular risk	Glimepiride has a cardio-safe profile compared to other SUs.
Impairment of ischemic preconditioning	Ischemic preconditioning of cardiac myocytes is not impaired by glimepiride; it is safer to use in cardiac patients in comparison to other SUs.
Efficacy	Glimepiride controls hyperglycemic conditions more effectively, both as monotherapy and in combination with insulin or metformin.
Beta-cell failure	Glimepiride improves insulin secretion and beta-cell failure in type 2 diabetes mellitus patients.
Insulin secretion phase differences	Glimepiride increases both first-phase and second-phase insulin secretion from beta-cells.
Weight disturbances	Compared to conventional SUs, glimepiride has been associated with least weight gain.
Safety to use with basal insulin	Glimepiride can be used in combination with basal insulin.
Cost of therapy	Compared to other oral antidiabetic drugs, SUs, including glimepiride, have low cost of therapy.
Pleiotropic effects	Glimepiride has several pleiotropic benefits, such as insulin sensitization of peripheral tissue, stimulation of lipogenesis and glycogenesis, and has anti-inflammatory, antioxidative and angiogenic properties.
PK/PD differences with other SUs	Compared to conventional SUs, glimepiride has lower incidence of hypoglycemia, more rapid onset of action, and shorter half-lives. Each SU has a unique PK/PD profile. Glimepiride is metabolized in the liver and excreted mainly through the renal system.
Effects of metabolites	Glimepiride is reported to be safer than other SUs, such as glibenclamide, in renal impairment patients who are at risk of hypoglycemia from active SU metabolites.
Use in special population	Unlike other SUs, glimepiride is well tolerated in various type 2 diabetes mellitus patients including the elderly, malnourished or debilitated patients. To avoid hypoglycemia, its use should be monitored in renal impairment patients.

SUs: Sulfonylureas; PK/PD: Pharmacokinetics/ Pharmacodynamics

carefully monitored in malnourished, elderly, or debilitated patients. It can also be used in patients with renal impairment with regular monitoring for signs and symptoms of hypoglycemia. In case of such symptoms, lower doses of glimepiride should be used.[1]

The common myths and facts regarding the safety, efficacy, and usage of glimepiride have been summarized in Table 1.

Conclusion

Sulfonylureas including glimepiride have been associated with several myths, which hinder their appropriate usage in type 2 diabetes mellitus patients. The common myths associated with the usage of glimepiride are adverse hypoglycemic effects, increased cardiovascular risk, weight-gain issues, safety in special populations, and effects of its metabolites. In spite of all these myths, among different types of SUs, glimepiride is reported to be relatively safe for use across different types of patients with type 2 diabetes mellitus, even in case of special populations like those at cardiovascular risk.

Conflict of Interest

AA is an employee of Sanofi India. All other authors report no conflicts of interest.

Funding

This initiative was supported by Sanofi India. All authors had full access to the chapters of the supplement and take complete responsibility for the integrity and accuracy of the content presented herein.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, reviewed and have given their approval for the final version to be published.

Acknowledgements

We thank Dr. Shalini Menon from Sanofi India for her constructive inputs, critique and periodic review on the supplement. Medical writing and editorial support were provided by Dr. Rajshri Mallabadi and Dr. Kavitha Ganesha of BioQuest Solutions Pvt. Ltd. which was paid for by Sanofi, India. Editorial support was also provided by Ms. Anahita Gouri and Dr. Rohan Mitra from Sanofi India.

References

1. Basit A, Riaz M, Fawwad A. Glimepiride: Evidence-based facts, trends, and observations (GIFTS). *Vasc Health Risk Manag* 2012; 8:463-472.
2. Kalra S, Bahendeka S, Sahay R, *et al*. Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of type 2 diabetes mellitus – International Task Force. *Indian J Endocrinol Metab* 2018; 22:132–157.
3. Kalra S, Madhu SV, Bajaj S. Sulfonylureas: Assets in the past, present and future. *Indian J Endocrinol Metab* 2015; 19:314–316.
4. Rosenstock J, *et al*. CAROLINA®: Cardiovascular safety and renal microvascular outcome with linagliptin in patients with T2D at high vascular risk. Oral presentation at the 79th Scientific Sessions of the American Diabetes Association (ADA), Monday, 10 June 2019, 16:30–18:30, San Francisco, CA, USA.
5. Zhu H, Zhu S, Zhang X, *et al*. Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials. *Diabetol Metab Syndr* 2013; 5:70.
6. Devarajan TV, Venkataraman S, Kandasamy N, *et al*. Comparative Evaluation of Safety and Efficacy of Glimepiride and Sitagliptin in Combination with Metformin in Patients with Type 2 Diabetes Mellitus: Indian Multicentric Randomized Trial – START Study. *Indian J Endocrinol Metab* 2017; 21:745–750.
7. Khunti K, Chatterjee S, Gerstein HC, Zoungas S, Davies MJ. Do sulphonylureas still have a place in clinical practice? *Lancet Diabetes Endocrinol* 2018; 6:821–832.
8. Yokoyama H, Sone H, Yamada D, *et al*. Contribution of glimepiride to basal-prandial insulin therapy in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2011; 91:148–153.
9. Kalra S, Das AK, Baruah MP, et al. Glucocrinology of modern sulfonylureas: clinical evidence and practice-based opinion from an international expert group. Diabetes Ther 2019. doi:10.1007/s13300-019-0651-1. [Epub ahead of print]
10. Gudipaty L, Rosenfeld NK, Fuller CS, *et al*. Effect of exenatide, sitagliptin, or glimepiride on β-cell secretory capacity in early type 2 diabetes. *Diabetes Care* 2014; 37:2451–2458.
11. Gerich JE. Is reduced first-phase insulin release the earliest detectable abnormality in individuals destined to develop type 2 diabetes? *Diabetes* 2002; 51(Suppl 1):S117–121.
12. Kabadi MU, Kabadi UM. Effects of glimepiride on insulin secretion and sensitivity in patients with recently diagnosed type 2 diabetes mellitus. *Clin Ther* 2004; 26:63–69.
13. Korytkowski M, Thomas A, Reid L, *et al*. Glimepiride improves both first and second phases of insulin secretion in type 2 diabetes. *Diabetes Care* 2002; 25:1607–1611.
14. Janka HU, Plewe G, Riddle MC, *et al*. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 2005; 28:254–259.
15. Ikuko Nakamura et al. Possible effects of glimepiride beyond glycemic control in patients with type 2 diabetes: a preliminary report. *Cardiovasc Diabetol* 2014; 13:15.
16. Kumar R, Kerins DM, Walther T. Cardiovascular safety of anti-diabetic drugs. *Eur Heart J Cardiovasc Pharmacother* 2016; 2:32–43.