GUEST EDITORIAL

Modern Sulfonylureas, Modern Science

SANJAY KALRA[*], SAURAV KHATIWADA[†], MANILKA SUMANATILAKE[‡], TINT SWE LATT[#], MOHAMMAD WALI NASERI[¥], GURU DHAKAL[§], PAYAL CHINTARAM[^], FARIA AFSANA[¶]

[*]Dept. of Endocrinology, Bharti Hospital, Karnal, India; University Center for Research & Development, Chandigarh University, Mohali, India
[†]Endocrine Unit, Dept. of Medicine, Chitwan Medical College, Bharatpur, Nepal
[‡]Dept. of Endocrinology, National Hospital of Sri Lanka, Colombo, Sri Lanka
[#]President, Myanmar Society of Endocrinology and Metabolism, Yangon, Myanmar
[¥]Dept. of Internal Medicine, Division of Endocrinology, Metabolism and Diabetes, Kabul University of Medical Sciences, Kabul, Afghanistan
[§]Dept. of Medicine, Jigme Dorji Wangchuck National Referral Hospital; Dean, Faculty of Postgraduate Medicine, Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan
[^]Dept. of Endocrinology, Dr AG Jeetoo Hospital, Port Louis, Mauritius
[¶]Dept. of Endocrinology, BIRDEM General Hospital, Dhaka, Bangladesh

Changing Times

Over the past century, diabetes has grown into a pandemic[1]. Newer facets of its causation, clinical presentation, complications and comorbidities are being unraveled. Simultaneously, newer means of treatment are being discovered. While these advances are more than welcome, this diachronicity comes with added responsibility.

The diabetes care professional needs to use newer, as well as conventional, therapies in a logical manner. Rational combinations should be used, keeping the etiopathogenesis of the disease, and the mechanism of action of drugs, in mind. The ever-increasing number of drug classes, drugs, and their preparations[2], however, make this easier said than done.

Consistency During Change

One class of drugs, which has served diabetes care consistently over more than half a century, is the unparalleled sulfonylureas. Along with metformin, a nearly 75-year-old classic, these drugs have offered efficacy in glucose control[3]. Used in type 2 diabetes, traditional sulfonylureas have been replaced by modern sulfonylureas, such as glimepiride and gliclazide MR. These drugs are listed in the World Health Organization's List of Essential Medicines, as well as in most national lists of essential drugs[4].

Classic Evidence

Modern sulfonylureas are an important option for second line management of diabetes, along with metformin and lifestyle modification. The "safe and smart" South Asian consensus, published a decade ago[5], remains a sempiternal publication in the field of sulfonylurea pharmacology. Trials such as ADVANCE, and Steno-2 have demonstrated the efficacy, safety and tolerability of gliclazide MR as part of a comprehensive management strategy[6,7]. ADVANCE ON and Steno-2 data have revealed the long-term benefits of such therapy in improving vascular health[8,9]. It must be noted that these trials were planned and executed much before the "wave" of regulator-mandated cardiovascular outcome trials (CVOTs) began. One such CVOT, the CAROLINA trial, was able to show that glimepiride was non-inferior to linagliptin in terms of cardiovascular outcomes[10]. Other CVOTs, which have demonstrated safety or benefit of drug classes such as dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP1RA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i), have also been designed on a framework of standard of care, which includes sulfonylureas[11]. The sulfonylureas in fact, have been described as glucocidal, rather than glucostatic drugs (personal communication). This reflects their potency as glucose-lowering drugs.

Contemporary Data

Glimepiride is the most frequently prescribed glucose-lowering drug in India, after metformin. Therefore, the three real world evidence (RWE) trials that we feature in this issue of *Asian Journal of Diabetology* are of great relevance to our readers.

George J et al describe the patterns of usage of glimepiride + metformin fixed dose combination (FDC) based upon retrospective analysis of records of 6,250 persons living with diabetes, treated by 500 health care professionals across India. The FDC was able to achieve an HbA1c reduction of >1%, with minimal hypoglycemia. Other drugs, such as DPP4i, GLP1RA, SGLT2i, pioglitazone, alpha-glucosidase inhibitors, and insulin were used in combination with glimepiride + metformin FDC. The commonest of these were DPP4i, highlighting the versatility and safety of this class of drugs *(George J et al. p 31)*.

At times, however, DPP4i therapy may be inadequate. George J et al studied the effects of shifting from DPP4i to modern sulfonylureas + metformin combination. They reported a 1.11% reduction in HbA1c, along with a 41.77 mg% and 67.39 mg% improvement in fasting and postprandial glucose values. This study demonstrates the utility of modern sulfonylurea + metformin in managing type 2 diabetes characterized by DPP4i inadequacy. The analysis also documented the relative use of various DPP4i: 50% prescriptions were of vildagliptin, followed by 30.2% of sitagliptin *(George J et al. p 9)*.

Conclusion

These studies highlight the contemporary importance of modern sulfonylureas in the management of type 2 diabetes. Continued, and concerted, efforts at continuing medical education are required, however, in order to maximize the benefit of this class of drugs. The concept of sulfonylurea stewardship, as described in this issue *(page 9)*, should be popularized in a manner similar to that of antibiotic or steroid stewardship. Rational and responsible use of modern sulfonylureas will improve glycemic control, and enhance long-term outcomes in persons living with type 2 diabetes. We commend George J, Aushili M, and their teams of investigators, for having highlighted the role of glimepiride + metformin combination in the modern management of type 2 diabetes.

References

1. Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023;11(7):474-89.
2. Kalra S, Baruah MP, Sahay R, Kishor K. Pentads and hexads in diabetes care: numbers as targets; numbers as tools. Indian J Endocrinol Metab. 2017;21(6):794-6.
3. Kalra S, Bahendeka S, Sahay R, Ghosh S, Mohammed F, Orabi A, 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(1):132-57.
4. Reddy A. Diabetes and the WHO model list of essential medicines. Lancet Diabetes Endocrinol. 2022;10(1):20-1.
5. Kalra S, Aamir AH, Raza A, Das AK, Khan AA, Shrestha D, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: a consensus statement. Indian J Endocrinol Metab. 2015;19(5):577-96.
6. Zoungas S, Chalmers J, Kengne AP, Pillai A, Billot L, De Galan B, et al. The efficacy of lowering glycated haemoglobin with a gliclazide modified release-based intensive glucose lowering regimen in the ADVANCE trial. Diabetes Res Clin Pract. 2010;89(2):126-33.
7. Pedersen O, Gæde P. Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the Steno-2 study. Metabolism. 2003;52(8 Suppl 1):19-23.
8. Wong MG, Perkovic V, Chalmers J, Woodward M, Li Q, Cooper ME, et al. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. Diabetes Care. 2016;39(5):694-700.
9. Gæde P, Oellgaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving HH, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia. 2016;59(11):2298-307.
10. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA. 2019;322(12):1155-66.
11. John M, Unnikrishnan AG, Kalra S, Nair T. Cardiovascular outcome trials for anti-diabetes medication: A holy grail of drug development? Indian Heart J. 2016;68(4):564-71.