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A Study Of Adverse Drug Reactions On The Newer Oral Antihyperglycemic Drugs Used In The Management Of Type 2 Diabetes Mellitus In Tertiary Care Hospital In Visakhapatnam

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Abstract

This study investigates about the adverse drug reactions associated with the newer oral anti hyperglycemic drugs (Gliptins and glifozins were studied mainly and their combination with other oral anti hyperglycemic drugs like Biguinides(metformin) and Sulfonyl urea drugs(glibemclemide, glipizide etc). The study has been conducted by the Department of Pharmacology, in association with Department of General Medicine and Endocrinology in Andhra Medical College, King George Hospital, Visakhapatnam, Andhra Pradesh after taking approval from the Institutional Ethics Committee. The study design is a hospital based cross sectional observational study The study population comprises of the type II diabetes mellitus patients visiting the outpatient clinic and inpatient unit wards of General Medicine and Endocrinology departments in King George Hospital. Out of 69ADRs reported, majority of theADRs42(60.87%) were found in male. Adults were more affected by ADRs 57(82.61%), followed by geriatrics 11(15.94%). The most common organ/system affected by ADRs was CNS 18(26.09%) followed by CNS and GIT 13(18.84%) and CNS and psychiatric symptoms 4(5.8%).the drugs which are suspected for causing ADRs in the study were as follows. 53(25.85%) of ADRs were contributed by Metformin either single or as a combination. 41(20.00) and 27(13.17%)were caused by Teneligliptin and Atorvostatin respectively.26 (12.68%) were caused by Telmisartan followed by 14(20.00%) caused by Vildagliptin. 13 (6.34%) was caused by Glimepiride. 10(4.88%) was caused each by Dapagliflozin and Rosuvastatin. 4(1.95%) each was caused by Sitagliptin and Canagliflozin. Most commonly reported ADR was headache28(40.58%) followed by pain during micturition 13(18.84%), weakness7(10.14 %)and polyuria6(8.70%).There is rapid and accelerated progress in the antidiabetics drugdevelopment front that runs parallel to our ever-evolving comprehension of the pathophysiology of diabetes. The recent safety concerns over glitazones, gliptins and their combinations in geriatric population should remind all physicians using new drugs for any chronic disease that longterm pharmacovigilance is necessary, and long-term outcome studies are required to evaluate the effects of mortality and morbidity. Hence the current study aims in evaluating the group wise distribution, type and severity of adverse drug reactions occurring in those using newer oral anti hyper glycemic drugs

Keywords: Adverse drug Reactions, Oral anti hyperglycemic drugs, Type 2 Diabetes Mellitus

Introduction

Diabetes Mellitus (DM)[1] is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyper glycaemia, or raised blood sugar, is a common effect of uncontrolled

diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. In majority of patients' anti hyperglycemic drugs remain the primary agents in management of DM. Currently there are variety of new drugs are approved in management of DM of which safety is established in clinical trials but their pharmacovigillance is needed for generating valid data. This disease involves multiple casual factors and clinical aspects, all of which should be well understood for better management. Metformin is the first-line pharmacotherapy recommended for glycemic control in patients with type 2 diabetes and has proven efficacy in achieving clinically relevant reduction in glycated hemoglobin (HbA1c) levels. Most patients eventually require treatment with 2 or more anti diabetes agents to maintain adequate control of blood glucose levels, and international treatment guidelines recommend stepwise intensification of therapy through add-on to metformin[2]. Incretin are hormones secreted from gastrointestinal tract which enhance insulin secretion in a glucose dependent manner. Strategies that target the gut derived incretin hormones glucagon-like peptide-1 (GLP-1) & glucose-dependent insulinotropic polypeptide (GIP) have led to emergence of newer segment of antidiabetic drugs like the dipeptidyl peptidase-4(DPP-4) inhibitors[3] and SGLT2 inhibitors (Gliflozins).

Dipeptidyl peptidase-4(DPP-4) inhibitors like Sitagliptin, Linagliptin, Saxagliptin, Vildagliptin, etc., prevent rapid inactivation of GLP-1 and GIP by the enzyme DPP-4, thereby enhancing their effect. The latest generation of oral anti diabetes drugs, dipeptidyl inhibitors, has demonstrated efficacy and safety in patients with inadequate glycemic control with metformin monotherapy[4]DPP-4 inhibitors have been considered as a cornerstone in the management of T2DM because of their robust efficacy and favorable tolerability profiles[5].European population that showed addition of teneligliptin either to glimepiride or metformin monotherapy led to significant reduction in HbA1c without increasing the risk of hypo glycaemia[6].

Intestines predominantly sport SGLT1 whereas the proximal tubules of the nephrons display both SGLT2 and SGLT1. A sodium-to-glucose cotransport ratio of SGLT1 is 2:1 and that of SGLT2 is 1:1 and while the former contributes 2% to glucose reabsorption, the latter contributes 98%.[25] Hence SGLT2 inhibition enables us to considerably reduce transcellular epithelial glucose reabsorption.

The progressive nature of type 2 diabetes requires a combination of two or more oral drugs in the long term. Safety and tolerability often limit the optimal use of Oral anti hyperglycemic drugs. Adverse drug reaction [7]is defined by WHO as any response to a drug which is noxious and unintended, and which occurs at doses used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. Adverse Drug Reaction (ADR) in the type-2 diabetes mellitus has been taken as subject for this study. Since Type 2 diabetes is the predominant form of diabetes and account for at least 90% of all cases of diabetes mellitus it is of great importance to study for the adverse drug reactions of newer oral anti hyperglycemic drugs. Hence the current study aims in evaluating the group wise Distribution type and severity of newer oral anti hyperglycemic drugs.

Materials And Methods

The study has been conducted by the Department of Pharmacology, in association with Department of General Medicine and Endocrinology in Andhra Medical College, King George Hospital, Visakhapatnam, Andhra Pradesh after taking approval from the Institutional Ethics Committee. The study has been conducted in accordance with the Principles of Good Clinical Practice(GCP)[8]

Study design: Hospital Based Cross Sectional Observational study.

Study population: The type II diabetes mellitus patients visiting the outpatient clinic and inpatient unit wards of General Medicine and Endocrinology departments in King George Hospital.

Study period: 3 months. (May 26th 2021 to August 26^{th,} 2021)

Sample method: convenience sampling.

Sample size: minimum 60.

Inclusion Criteria:

1. Age group more than 18 years, both sexes, diagnosed with type 2 diabetes mellitus alone or diabetes mellitus with other disease and who are on newer oral anti hyper glycemic

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drugs as either mono therapy or combination therapy.
2. Patients who are taking at least one newer oral anti hyperglycaemic drug.
3. Those Patients who voluntarily reported an ADR or is the case of an ADR related admissions
4. Those who given valid informed consent.

Exclusion Criteria:

1. Newly diagnosed naive diabetic patients.
2. Seriously ill patients.
3. Patients with gestational diabetes.
4. Patient on herbal drugs or drugs of abuse
5. Incomplete information given in the ADR forms.

Results And Discussions

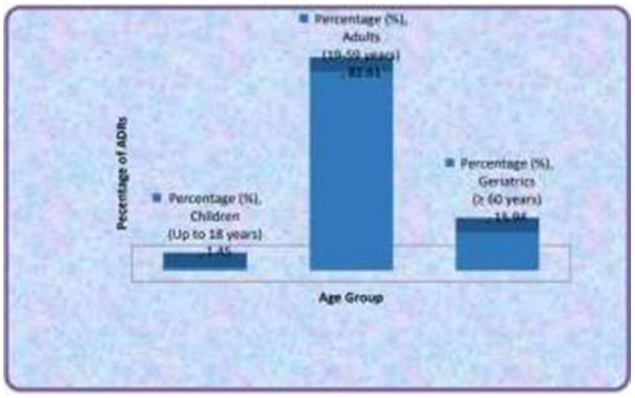
Gender wise distribution of ADRs

Out of 69ADRs reported, majority of theADRs42(60.87%) were found in male.

Adults were more affected by ADRs 57(82.61%), followed by geriatrics 11(15.94%).

Age Wise Distribution Of ADRs

AGE GROUP	NUMBER OF ADRs	PERCENTAGE (%)
Adults19-59 years)	58	84.05
Geriatrics(≥ 60 years)	11	15.94
Total	**69**	**100%**



Organ/System affected by ADRs

The most common organ/system affected by ADRs was CNS 18(26.09%) followed by CNS and GIT 13(18.84%) and CNS and psychiatric symptoms 4(5.8%). Three (4.35%) ADR reports were associated with dermatology, 4(5.8%) were associated with GIT and 6(8.7%) ADR reports were associated with metabolic system (mainly hypoglycemia), 2(2.9) were psychiatric and 19 (27.54%) renal system respectively.

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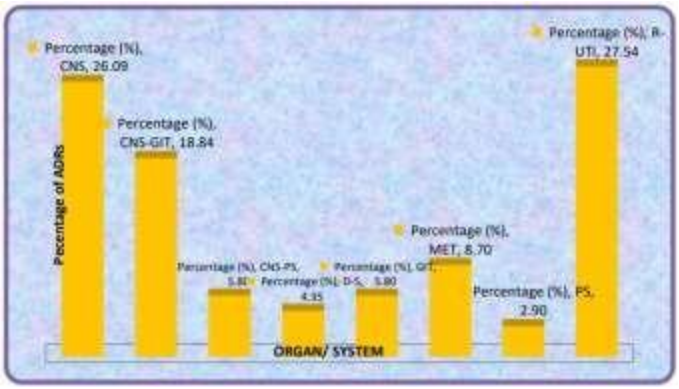
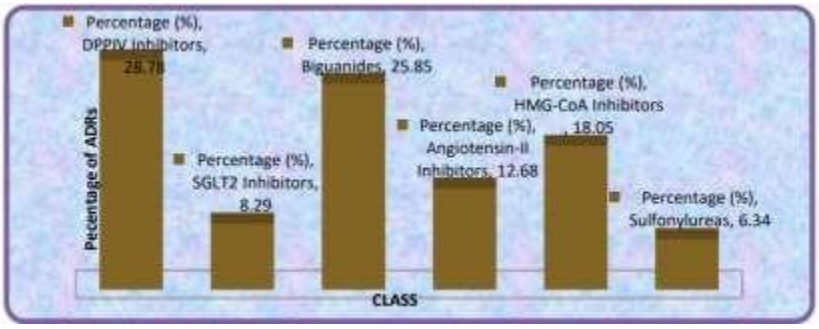


Therapeutic drug classes implicated to cause ADRs

The therapeutic class of oral anti diabetic drugs most commonly associated with ADRs was analyzed. Highest incidence of ADRs was noted with Dipeptidyl peptidase inhibitors in combination with Metformin (DPP IV - Met) 43(62.32%) followed by Sodium- Glucose co Transporter -2 inhibitors(SGLT-2) with Metformin11(15.94%) and DPP IV inhibitors8(11.59%) alone. Only 1(1.45%) ADR was reported to be a DPP IV with SGLT2 and Metformin.

Drugs Which Are Suspected For Causing ADRs

53(25.85%) of ADRs were contributed by Metformin either single or as a combination. 41(20.00) and 27(13.17%)were caused by Teneligliptin and Atorvostatin respectively.26 (12.68%) were caused by Telmisartan followed by 14(20.00%) caused by Vildagliptin and 13 (6.34%) was caused by Glimepride . 10(4.88%) was caused each by Dapagliflozin and Rosuvastatin. 4(1.95%) each was caused by Sitagliptin and Canagliflozin.



Predisposing factors involved in development of ADRs

Polypharmacy 69(41.07%), underlying disease/co morbidity 63(37.50%) ,female gender 27(16.07 %) and Geriatric population 9(5.36) were some of the pre disposing factors involved in the development of ADRs.

Types Of ADRs

As per the WHO classification of Types of ADRs[9] ,out of the 69 reported ADRs,56(81.16%)ADRs were Type A reactions and 13(18.84%)were Type B reactions

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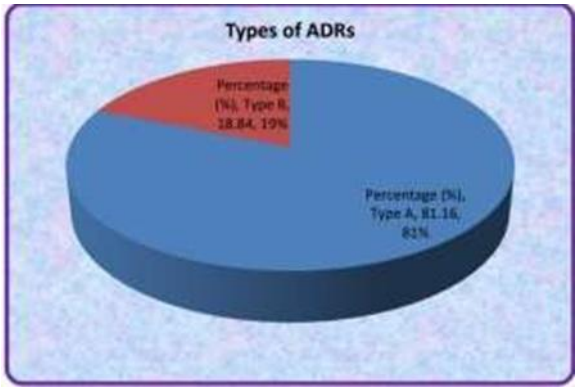

Details Of ADRs

Most commonly reported ADR was headache28(40.58%) followed by pain during micturition 13(18.84%) ,weakness7(10.14 %)and polyuria6(8.70%).

Table : Details of ADRs

DETAILS OF ADRs	NUMBER OF ADRs	PERCENTAGE (%)
Abdominal Pain (ABDP)	1	1.45
Constipation (Const)	3	4.35
Depression(Depr)	2	2.90
Dizziness(Dizz)	3	4.35
Fatigue/Weakness(FAT)	7	10.14
Headache(Hache)	28	40.58
Pain during Micturition(PDM)	13	18.84
Polyuria(POU)	6	8.70
Redness of Skin(REDSK)	3	4.35
Weight Gain(WTG)	3	4.35
Total	**69**	**100%**

Management of ADRs

Fate of suspected drug(s)

Out of 69 ADRs, suspected drug was withdrawn in 7(10.14%) cases, there was no change in62(89.86%)cases. Alternate drug or dose alteration was not done with any ADR. Symptomatic treatment was given for 20(28.99%) ADRs and no treatment was given in49(71.01%).

Treatment of ADRs

Out of 69 ADRs, majority of the patients were given no treatment 49(71.01%) and only 20(28.99%) were given symptomatic treatment.

Outcome of ADRs

Majority42(60.87%) of the patients who experienced ADRs were recovered.

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27(39.13%) of patients continued to experience ADRs.

Severity of ADRs

The reported ADRs were categorized Using Hartwig's severity scale. Maximum reported ADRs 51(73.91%) were mild in nature whereas remaining 18(26.09%) ADRs were moderate in nature.

Causality Assessment OF ADRs

Causality assessment of ADRs was carried out using WHO probability scale. As per WHO probability scale, majority of ADRs 54(78.26%) were 'Possible' followed by 'Probable' 15(21.94%) .

Table : Causality assessment of ADRs - WHO probability scale

PROBABILITY SCALE	NUMBER OF ADRs	PERCENTAGE (%)
Certain	0	0.00
Probable	15	21.74
Possible	54	78.26
Unlikely	00	00.00
Conditional	00	00.00
Unassessable	00	00.00
Total	69	100%

Discussion

In the present study, a total of 69 ADRs were reported during the study period with male (60.87%) predominance over female (39.13%) which is contrary to the study conducted by Tirthankar Debet et al.[9] . Patients in the Age group of 19-59 years experienced maximum ADRs (82.61%), which is in accordance with the study of Bhattacharjee et al [10] which shows that the incidence of ADR is more in adult population. Geriatric (>60 years) also there was considerable number of ADRs i.e. about 15.94% which was in accordance with Bhattacharjee et al [10]. Organ /system most commonly affected was Renal-Urinary tract infections (27.54%) followed by CNS(26) ADRs which was similar to the study conducted by Singh H et al [11] The most commonly identified therapeutic class of oral anti diabetic agents that caused ADRs were the Combination of DPP IV inhibitors with Biguanides (62.32) followed by SGLT 2 with Biguanides (15.94%), DPP IV (11.59%), SGLT2 inhibitors(8.7%) and combination of SGLT 2 inhibitors with DPP IV and Biguanides (1.45%) whereas the Tirthankar Debet et al [9] study showed that Biguanides monotherapy followed by Sulfonylureas, Thiazolidinediones (TZD), DPP-4 inhibitors, Alpha-glucosidase inhibitors and SGLT2 inhibitors were the ADR causing group of drugs. The drugs suspected to be responsible for ADRs in our study were Metformin either single or as combination (25.85%) followed by Teneligliptin (20%) and Atorvostatin (13.17%) which was partially similar to the study by Alex et al.[12] 36 Polypharmacy has been shown to intensify health care utilization and increase medical care costs for patients with diabetes and risk of ADR is also increased manifold. In the present study, predisposing factors involved in development of ADRs is mainly due to polypharmacy due to underlying co morbid conditions (41.07%), underlying disease (37.50%) female patients (16.07%) and geriatric population (5.36%) which was similar to Alex et.al study [12] . Mostly, type A adverse drug reactions were reported among the cases which was in concurrence with the study by Bhattacharjee et al [10] . The most commonly reported ADR was headache (40.58%) followed by pain during micturition (18.84%) which were contrary to the Javedh Shareef et al [13] study as their study showed hypoglycemia followed by

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gastrointestinal symptoms as the most common ADR. In our study, as a part of management of the adverse drug reactions, either the drug was withdrawn (10.14%) or there is no change in the fate of the suspected drug which was contrary to the study by Javedh Shareef et al where the drug was withdrawn in majority of cases. Regarding the treatment of ADRs, no treatment (71.01%) was instituted in majority of patients as the symptoms were mild in severity which is similar to the Bhattacharjee et al [10] . On the evaluation of the severity of ADRs by the Hartwig and Siegel severity assessment scale, it was evident that most of the ADRs reported in the study were mild (73.91%) in nature followed by moderate (26.09%) . No lethal outcomes were observed during the study period. This was similar to the Alex et al study .[12]

Conclusion

In order to safeguard and protect the health of the community, Pharmacovigilance Programme of India (PvPI) is implemented and the monitoring body is National Coordinating Centre, Indian Pharmacopoeia Commission (IPC), In India. Adverse drug reactions are reported to NCC PvPI which are then directed towards WHO Uppsala Monitoring Centre (UMC) Sweden which is the global monitoring centre for worldwide data. Central Drugs Standard Control Organization (CDSCO) is the regulatory authority of India under the Directorate General Health Services, Ministry of Health and Family Welfare (MOHFW), Government of India. This article focusses on the various strands of pharmacovigilance of newer oral Diabetic Drugs at the healthcare professional and consumer level. It also discusses the lacunae in the execution of pharmacovigilance thus helping in enhancing the quality of health safety. Even a minuscule contribution by a health care professional or a consumer can voluminously help in promotion of drug safety. Therefore, there is a need of inculcating the culture of adverse drug reaction reporting for the welfare of the vulnerable masses.

There is rapid and accelerated progress in the antidiabetics drug-development front that runs parallel to our ever-evolving comprehension of the pathophysiology of diabetes. Clinicians need to be abreast of this plethora of newer antidiabetic drugs coming up, their efficacy, adverse effect profile and stand in diabetes management that empowers them to better manage diabetes.

The recent safety concerns over glitazones, gliptins and their combinations in geriatric population should remind all physicians using new drugs for any chronic disease that long-term pharmacovigilance is necessary, and long-term outcome studies are required to evaluate the effects of mortality and morbidity.

Avoidable ADR can be reduced by more skillful prescribing. Providing knowledge and awareness of ADRs reporting among health care professionals would introduce the reporting among medical practitioners and increase the reporting rates of ADRs. Careful involvement in planning and monitoring of drug therapy will lead to prevention of ADRs. This study suggests that ADR in hospital-based monitoring is a good method to detect known and unknown links between drug exposure and ADRs. A good relationship also needs to be framed between doctors and pharmacovigilance centers so that they consider ADR reporting as an integral part of their clinical activities. It is needed to make aware the treating doctors about the importance of observing for ADR, recording them continuously and reporting them to the concerned authority. This practice will prove to be very valuable in making the drug therapy safer and rational. In future a comprehensive Programme is required in each level of health care system starting with treating doctors, nurses, paramedics and drug dispensing pharmacist to ensure better and safe pharmacotherapy and improve compliance of patients. New medications should be prescribed cautiously with clear therapeutic goals and recognition of the impact a drug can have on multiple organ systems. Prescribers should regularly review medication efficacy and be vigilant for ADRs and their contributory risk factors. Deprescribing should occur at an individual level when drugs are no longer efficacious or beneficial or when safer alternatives exist. Inappropriate prescribing and unnecessary polypharmacy should be minimized. Comprehensive geriatric assessment and the use of explicit prescribing criteria can be useful in this regard.

References

1. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a

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collaborative meta-analysis of 102 prospective studies. Emerging Risk Factors Collaboration.
2. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary. EndocrPract. 2017;23(2): 207-238.
3. Bohannon N. Overview of the gliptin class (dipeptidyl peptidase-4 inhibitors) in clinical practice. Postgrad Med. 2009;121(1):40-5 Waget A, Cabou C, Masseboeuf M, Cattan P, Armanet M, Karaca M, et al. Physiological and pharmacological mechanisms through which the DPP-4 inhibitor sitagliptin regulates glycemia in mice. Endocrinology. 2011;152(8):3018-29
4. Taskinen MR, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, doubleblind, placebo-controlled study. Diabetes ObesMetab. 2011;13:65-74
5. Deacon, C. (2011). Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. Diabetes Obes. Metab. 2011;13:7-18.
6. Bryson A, Jennings P, Deak L, Paveliu F, Lawson M. The efficacy and safety of teneligliptin added to ongoing metformin monotherapy in patients with type 2 141 diabetes: a randomized study with open label extension. Expert Opinion on Pharmacotherapy. 2016;17(10):1309-16.
7. Aronson JK. Ferner RE. Clarification of terminology in drug safety. Drug Saf. 2005; 28:851–70. [PubMed] [Google Scholar]
8. "ICH Official web site : ICH". www.ich.org. Retrieved 2021-11-24
9. Tirthankar D, Abhik C, Abhishek G. Adverse drug reactions in Type 2 diabetes mellitus patients on oral antidiabetic drugs in a diabetes outpatient department of a tertiary care teaching hospital in the Eastern India. International Journal of Medical Science and Public Health. 2016;6(3):554-7
10. Bhattacharjee A, Gupta MC. Agrawal S. Adverse drug reaction monitoring of newer oral anti diabetic drugs-a pharmacovigilance perspective. International Journal of Pharmacological Research. 2016;6(4):142-51
11. Singh H, Dulhani N, Kumar BN, Singh P, Tewari P, Nayak K. A Pharmacovigilance Study in Medicine Department of Tertiary Care Hospital in Chhattisgarh (Jagdalpur), India. J Young Pharm. 2010;2(1):95-100..
12. Alex, S. M., S. Bs, S. S, J. Kn, A. S. Menon, and U. D. P. “drug utilization pattern of antidiabetic drugs among diabetic outpatients in a tertiary care hospital”. Asian Journal of Pharmaceutical and Clinical Research, vol. 8, no. 2, Mar. 2015, pp. 144-6
13. Javedh S, Jennifer F, Laxminarayana S, Shifaz AK. A Study on Adverse Drug Reactions In Hospitalized Patients With Diabetes Mellitus in A Multi-Specialty Teaching Hospital. Asian Journal of Pharmaceutical and Clinical Research. 2016;9(2):114-7

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