ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

Evaluation of Prescribing Practices of Metformin in Patients with Type-2 Diabetes Mellitus

P. Maheshwari*, T. S. Shanmugarajan
Department of Pharmacy Practice, School of Pharmaceutical Sciences, VISTAS, Pallavaram, Chennai-600117, Tamilnadu, India
*Corresponding Author E-mail: **mahe.mpharm@gmail.com**

ABSTRACT:

Objectives: To evaluate the prescribing patterns of metformin in patients with type-2 diabetes mellitus and determine whether they are in accordance with published contraindications and precautions. **Methods:** Medical records of patients admitted with type-2 diabetes mellitus, who received at least one dose of metformin were identified and enrolled into the study. Patient demographic, clinical and biochemical data pertaining to diabetes and its risk factors were collected and documented. Prescribing patterns of metformin in these patients wereevaluated using the drug chart. All the prescriptions were checked for its accordance with published contraindications and precautions. Prescriptions in patients with type-2 diabetes mellitus were compared to the standard prescribing guidelines as per American Diabetes Association to analyse its compliance with recommended guidelines to determine whether metformin was prescribed to patients possessing any of the risk factors associated with development of lactic acidosis. **Results:** Metformin was used as the first line therapy in 138 patients with type 2 diabetes mellitus, either as mono-therapy or at some instances in combination with other oral hypoglycaemic agents or insulin. About 56 patients were found to have either one or more absolute contraindications and 113 patients had precautionary conditions, despite which the therapy was continued in about 89.13% of the patients. **Conclusion:** The prescribing contraindications of metformin were found to be high and hence it is necessary to create awareness regarding contraindications and precautionary conditions regarding metformin among physicians and other health care professionals so as to prevent the incidence ling tern adverse effects like lactic acidosis.

KEYWORDS: Metformin, Diabetes mellitus, lactic acidosis, prescribing practice, prescribing contraindications.

INTRODUCTION:

Diabetes mellitus (DM) is known to be an important cause of premature death and disability[1] and is one of the four priority non communicable diseases (NCDs) targeted by world leaders in the 2011 Political Declaration on the Prevention and Control of NCDs[2]. Type 2 diabetes mellitus (DM), also known as non-insulin dependent diabetes mellitus (NIDDM) is a long term metabolic disorder mainly characterized by insulin resistance and a relative lack of insulin secretion.

Received on 18.09.2018 Modified on 16.10.2018
Accepted on 03.11.2018
Research J. Pharm. and Tech 2019; 12(2):531-534.
DOI: 10.5958/0974-360X.2019.00093.3

In addition, it may also be associated with 'insulin resistance syndrome' which includesobesity, hypertension, dyslipidemia, and elevated inhibitor plasminogen activator-1 (PAI-1) levels. Because of these abnormalities, patients with type 2 diabetes are at increased risk of developing macrovascular complications[3]. Type 2 DM accounts for as much as 90% of all cases of DM, and the estimated prevalence of type 2 DM in the United States was about 8.7% in persons aged 20 years and older[1,4].

As per the fact sheet released by the Arogya World, diabetes is a huge problem in India[5]. The prevalence of diabetes mellitus had increased tenfold, from 1.2% to 12.1%, between 1971 and 2000[6]. As per 2011 census,

61.3 million people aged 20-79 years live with diabetes in India which had gradually increased to 422 million in 2014. This population is expected to increase to 101.2 million by 2030[7]. In 2012, 1.5 million deaths were reported worldwide due to diabetes. It was the eighth leading cause of death among both sexes and the fifth leading cause of death in women in 2012[8,9].

If the A1c target is not achieved after approximately 3 months, it is advised to consider a combination of metformin and one of the six available treatment options: sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose cotransport-2 (SGLT-2) inhibitor, glucagon-like peptide (GLP-1) receptor agonist, or basal insulin. If A1c target is still not achieved after 3 months of dual therapy, three-drug combination is recommended. If A1c target is still not achieved after 3 months of triple therapy, proceed to combination injectable therapy[3].

MATERIALS AND METHODS:

Based on the inclusion and exclusion criteria, 138 patients with type 2 DM and prescribed with metformin, both as single drug therapy or in combination with other anti-diabetic agents were enrolled into the study. A structured and validated case report form was used to collect the required demographic, clinical and biochemical date. the drug chart of the patients were evaluated for the presence of absolute contraindications and precautionary conditions, as mentioned in the metformin package insert or information leaflet and also as per the recently updated standard ADA guidelinesThe data were compiled in Microsoft Excel sheet and the mean, median and standard deviation of age were calculated. The remaining results were interpreted with the help of tables and graphs.

RESULTS:

Table 1: Age Wise Distribution of Patients with Type-2 DM

S. No.	Age	Males	Females	Total
1	18-40	08	8	**16**
2	40-60	42	30	72
3	60-80	18	26	**44**
4	≥80	02	04	06
Total		70	68	138

Table 2: Prescribing Frequency of Metformin

Metformin	No. of Patients	Percentage (%)
Monotherapy	**111**	**80.43**
Sitagliptin + Metformin	16	11.59
Vildagliptin + Metformin	11	07.97

Table 3: Prescribing Frequency of Metformin in Different Hospital Service

Hospital Service	No. of Patients	Percentage (%)
General Medicine (Male)	58	42.03
General Medicine(Female)	60	43.48
Orthopaedics	2	1.45
Surgery (Male)	10	7.25
Surgery (Female)	8	5.79

Table 4: Summary of the Absolute Contraindications and Precautionary Conditions in Patients taking Metformin

Variable	No. of Patients	Percentage (%)
Absolute Contra-Indications 1. Elevated S.Creatinine Level	48	34.78
2. CHF	16	11.59
3. Contrast Dye	11	7.97
Precautionary Condition 1. Age ≥80 yrs.	6	4.35
2. Elevated AST/ALT	27	19.57
3. Cationic Drug Use	64	46.38
4. Excessive Alcoholism	49	35.51
5. Hypoxia - COPD - MI - Dehydration	 16 14 23	 11.59 10.14 16.67

Table 5: Frequency of Contraindications and Precautions in Patients taking Metformin

Variable	No. of Patients	Percentage (%)
No. of Contra-Indications 0 1 2	 80 39 19	 57.97 28.26 13.77
No. of Precautionary Condition 0 1 2 3 4	 25 47 34 21 11	 18.12 34.06 24.64 15.22 7.97

Table 6: Prevalence of Metformin Therapy Continuation Despite the Presence of an Absolute Contraindication or A Precautionary Condition

Variable	General Medicine	Surgery	Orthopaedics	Total
Absolute Contra-Indications 1. Elevated S.Creatinine Level 2. CHF 3. Contrast Dye	 35 15 6	 0 0 2	0	 35 15 8
Precautionary Condition 1. Age ≥80 yrs. 2. Elevated AST/ALT 3. Cationic Drug Use (Ranitidine) 4. Excessive Alcoholism 5. Hypoxia 6. Surgery	 6 21 47 41 59 0	 0 2 12 4 4 2	 0	 6 23 59 45 63 2

Table 7: Distribution of Diabetic Complications Among Patients

Complications	No. of Patients	% of Patients
Neuropathy	06	4.35
Foot ulcer	12	8.69
Nephropathy	42	30.43
Retinopathy	10	7.25
Cardiovascular risks	16	11.59
Nil	52	37.69

Table 8: Prescribing Frequency of Other Anti-Diabetic Agents

Drugs	No. of Patients	% of Patients
Sulfonyl ureas	26	23
Insulin	29	26
DPP-4 inhibitors	46	42
GLP-1 antagonist	01	1
Alpha-glycosidase inhibitors	09	08

RESULTS:

Around 138 patient case sheets were enrolled into the study based on the inclusion and exclusion criteria. All the patient's medical records were identified and subjected to data collection in order to analyse for the prescribing practise of metformin and its adherence to the guidelines and package inserts. The mean (±SD) age of the study population was 56.75±5.2 (Median-57, range 19-86) with greater number of males than females, but no signifaicant difference was noticed. Hence it cannot be said that sex of the patient plays a vital role in the onset of diabetes. Most of the patients were aged between 40-60 years. The age wise distribution of the patients receiving metformin, with respect to their gender is shown in (Table 1)

The study involved patients suffering from type-2 diabetes mellitus and prescribed metformin, for as long as 1-25 years. Only 26 (18.84%) patients were cases of newly detected type 2 DM. Metformin is the first line therapy for the treatment of type-2 DM, and were prescribed either as monotherapy or as fixed drug combinations (Table 2)

Most of the patients prescribed with metformin, either as monotherapy or combination therapy were from the department of general medicine- female (42.03%) followed by general medicine-female (43.48%). Other departments included surgery and orthopaedics (Table 3)

Metformin package insert dictates certain absolute contra-indications and precautionary conditions for the use of metformin in patientrs with type 2 DM. Out of all the 138 prescriptions evaluated, one or more absolute contraindications were present in 56 prescriptions whereas one or more precautionary condition were present in 113 prescriptions (Table 4 and 5)

Even in the presence of one or more contra-indications and precautionary condition, metformin was continued in most of the prescriptions. Metformin therapy was discontinued only in 15 (10.87%) prescriptions where absolute contraindications or precautionary conditions were present, and hence can be said to adhere with the guidelines. (Table 6)

Many patients diagnosed with type 2 DM were found to have associated complications the most common being diabetic nephropathy (30.43%) and the least to be diabetic nephropathy (4.35%). Most of the patients (33.34%) were not diagnosed with any comorbid conditions. The distribution of diabetic complications is depicted in (Table 7)

Only in 26 % 0f patients metformin was the only anti-diabetic agent to be prescribed. The rest of the prescriptions included a combination therapy with either other oral hypoglycemic agents or insulin. Oral hypoglycemic agents prescribed included DPP-4 inhibitors, sulfonylureas, GLP-1 agonist and α-glucosidase inhibitors (Table 8)

CONCLUSION:

Metformin is a widely used oral hypoglycemic agent and is the drug of choice for patients with type 2 DM, in the absence of contra-indications. Metformin associated lactic acidosis is known to be the most serious adverse effect when prescribed in the presence of precipitating factors, though there are no strong evidences to prove its incidence when prescribed in the absence of such contraindications, other than overdoses.

The study showed that the prescribing contraindications were quite high for metformin. Metformin is one of the most safe drug and hence it is continued to be used by the physicians even in the presence of its contra-indications. But lack of adherence to the guidelines may result in severe adverse effect, such as MALA. This may also be due to the lack of knowledge of the physician regarding the updated guidelines and hence it becomes the responsibility of the pharmacist to update the physician and promote the best patient care.

It remains important that physicians, nurse practitioners, physician assistants, and other health care professionals (including nurses and pharmacists) responsible for drug delivery remain aware of patient-specific factors that increase a patient's risk of MALA. Our analysis leads to the conclusion that metformin continues to be prescribed to patients who are at high risk for lactic acidosis. What is particularly alarming is the fact that the problem may be even more widespread than is evident from our data. The prevalence of risk factors in our study population was most likely underestimated for several reasons,

most having to do with the retrospective nature of the study design. The investigations for detecting MALA (blood pH, plasma lactate levels etc.) in such patients were not carried out. Hence the limitation of this study is that the actual prevalence for MALA in the patient population with risk factors could not be analysed.

It is also important to recognize that our study was designed neither to verify that metformin therapy causes lactic acidosis nor to suggest that metformin use should be avoided in all patients with relative precautions to the drug. Rather, we were interested in determining whetherprescribers were complying with the labelled contraindications and precautions to the use of metformin or adhering to the standard prescribing guidelines proposed by ADA. .In this regard, we determined that at the time of or some time during admission to the hospital, about 58 patients developed at least 1 absolute contraindication to the drug, and in most of these, metformin therapy was continued despite the contraindication. This failure to recognize contraindications was just as likely to occur on a medical service (by those who may be "routine prescribers" of metformin) as it was on a surgical service (by those who may be less familiar with the drug).

REFERENCE:

1. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999;131:281-303.
2. Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH. Evaluation of Prescribing Practices: Risk of Lactic Acidosis with Metformin Therapy. Arch Intern Med 2002,162:434-437.
3. Bennett WL, Maruthur NM, Singh S. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154: 602-613.
4. VijanS, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med2014,174:1227-1234.
5. Agarwal AA, Jadhav PR, Deshmukh YA. Prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients. J Basic Clin Pharm2014, 5(3):79-83.
6. Huang W, Castelino RL, Peterson GM. Metformin usage in type 2 diabetes mellitus: are safety guidelines adhered to.Intern Med J.2014;44(3):266-272.
7. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic acidosis in patients with diabetes treated with metformin. N Engl J Med1988;338(4):265-266.
8. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med2008; 359: 1577-1589.
9. Buse JB, Ginsberg HN, Bakris GL. American Heart Association. American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2007;30: 162-172.