



RESEARCH ARTICLE

Journal home page: www.jpadr.com

Metformin related adverse events: A prospective observational study in health care centers of western Odisha

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ARTICLE INFO ABSTRACT



Received 17 September 2020;
Revised 29 October 2020;
Accepted 23 November 2020.

Keywords:

Metformin, diabetes,
anti-diabetic therapy,
adverse events.

Introduction: The most common adverse drug reactions were lactic acidosis followed by hypoglycemia, hypersensitivity reactions, nausea, decreased appetite, vomiting, weakness, and diarrhea.

Objectives: The study was done to explore the management of the patients having diabetes by primary care physicians, and the adverse reactions associated with the dose regimens. This study provided information regarding the adverse drug reactions that could be developed in any patient and increases the risk to the patient.

Methods: A qualitative In-Depth Interview study was conducted among the primary care physicians at ten primary health care centers at Sambalpur city of Odisha, India. The data were analyzed using content analysis. This was a prospective observational study (March 2019 - September 2019) among diabetes patients receiving metformin. Data were collected and analyzed to find out the demographic characteristics, causality, and severity of adverse events with metformin regimens.

Results: It was seen that 8 % of cases could be assessed as certain and 24 % could be assessed as probable. Most (60 %) cases were assessed as possible. Severity assessment of ADRs by modified Hart wig and Siegel's severity Scale (n=143) indicates 64% of the case were mild and 34% of cases are moderately severe.

Conclusions: Hence with an aim of patient safety quality of the drug formulations has to be improved that could ultimately improve drug safety.

An official publication of Global Pharmacovigilance Society.

Introduction

Diabetes mellitus (DM) is a chronic, progressive, incompletely understood metabolic condition chiefly characterized by hyperglycemia and caused due to impaired insulin secretion, resistance to tissue actions of insulin, or a combination of both. Diabetes mellitus is a group of

metabolic disorders in which the blood glucose is higher than normal levels, due to insufficiency of insulin release or improper response of cells to insulin, resulting in high blood pressure. The resultant hyperglycemia produces the classical symptoms of polyuria, polydipsia, and polyphagia. It may also cause nerve problems, kidney problems, and blindness, loss of limbs, and sexual



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Available online 1 December 2020

dysfunction increase in a heart attack or stroke. With time, multiple glucose-lowering medications are commonly required to reduce and maintain plasma glucose concentrations within the normal range. Diabetes mellitus individuals also are at very high risk for microvascular complications and the incidence of heart attack and stroke is increased two- to three-fold compared with non-diabetic individuals. Therefore, when selecting medications to normalize glucose levels in DM patients, it is important that the agent not aggravate, and ideally even improve cardiovascular risk factors and reduce cardiovascular morbidity and mortality.

Metformin is the most commonly prescribed oral glucose-lowering agent worldwide and is recommended as first-line therapy by the American Diabetes Association (ADA), the European Association for the Study of Diabetes, and the International Diabetes Federation. Potential mechanisms for the putative protective effect of metformin include improved glycemic control, reduction in methylglyoxal levels, decrease in VLDL secretion and plasma triglyceride levels, and reduced postprandial lipaemia

Methods

The present study was conducted in the outpatient setting of ten numbers of health care centers at Sambalpur, Odisha. Data were collected from the patients on Metformin regimen during the study period. Written informed consent was taken from the patients after explaining the study procedure.

It was a prospective observational study for a period of seven months (March 2019 - September 2019) among patients living with diabetes and receiving ADT. A total of 1000 patients enrolled randomly for the study, from which 143 cases of ADRs were observed during the study period. These patients were intensively monitored for any adverse clinical events during follow-up visits to the health care center. Subjects of either sex, aged 0-80 years, receiving Metformin during March 2019 - September 2019 were included in the study. While the patients with any other comorbidity like hypertension, chronic kidney disease, and pregnant women were excluded from the study. Diagnosis of adverse events was made based on patient's complaints and/or from the patient's attendants, their morphological changes during routine clinical examinations as well as a review of outpatient case records, laboratory reports, clinician's notes, and prescriptions at each follow-up visit. All the information was recorded in the 'Suspected ADRs reporting form' designed by the Indian Pharmacopoeia Commission, Ghaziabad, India. Any other details regarding

drug therapy and associated adverse events were obtained from the treating physician. The WHO-UMC probability scale and Naranjo algorithm were used for causality assessment (Rath et al., 2020). The study was approved by the institutional ethics committee.

Statistical analysis

The obtained data were analyzed by descriptive statistical method and values are presented in numbers and percentages.

Results

During this study, it was observed that 143 patients were reported with adverse drug reactions. Most of the patients in the age group 41- 60 years were got affected with adverse drug reactions as given in **Table 1**. The adverse events were mostly observed in males as compared to females. The most common adverse drug reactions were lactic acidosis followed by hypoglycemia, hypersensitivity reactions, nausea, decreased appetite, vomiting, weakness, and diarrhea. The numbers of patients who suffered from adverse drug reactions were presented in **Table 2**. Other rare types of drug reactions such as Vitamin B12 deficiency, rash, painful urination, muscle pain, cough, lower back pain was observed in 3-4 patients. Causality assessment by using the WHO-UMC Scale (n=143). It was seen that 8 % of cases could be assessed as certain and 24 % could be assessed as probable. Most (60 %) cases were assessed as possible as given in **Table 3**. Severity assessment of ADRs by modified Hart wig and Siegel's severity Scale (n=143) indicates 64% of the case were mild and 34% of cases are moderately severe, as presented in **Table 4**.

Table 1: Age and gender distribution of individual case safety reports (n=143).

Characteristics	No. of patients	Percentage (%)
Age		
< 20 years	0	0
21 - 40 years	46	32.5
41 - 60 years	54	37.5
Above 60 years	43	30.0
Gender		
Males	85	59
Females	58	41

Table2: Reaction pattern distribution

Types of ADR	No. of cases	Percentage (%)
Abdominal discomfort	5	3
Cough	1	1
Decreased appetite	9	6
Diabetes worsening	3	2
Diarrhea	8	6
Edema	2	1
A general feeling of discomfort	6	4
Heart rate increased	6	4
Hypersensitivity reaction	10	7
Hypoglycemia	15	10
Lack of taste	5	3
Lactic acidosis	16	11
Lower back pain	1	1
Muscle cramp	4	3
Muscle pain	3	2
Nausea	10	7
Obesity	7	5
Painful urination	3	2
Rash	2	1
Sleepiness	5	3
Upset stomach	4	3
Vitamin B12 deficiency	2	1
Vomiting	8	6
Weakness	8	6
Total	143	

Table 3: Causality assessment by using WHO-UMC scale

Types of causality	No. of ADRs	Percentage
Certain	11	8
Probable	34	24
Possible	86	60
Unlikely	6	4
Conditional	3	2
Unassessable	3	2
Total	143	100

Table 4: Assessment of severity of ADRs

Severity	levels	Number of cases	Percentage
Mild	Level 1	9	6
	Level 2	34	24
	Level 3	49	34
Moderate	Level 4a	20	14
	Level 4b	29	20
	Level 5	3	2
Severe	Level 6	0	0
	Level 7	0	0
Total		143	100

Discussion

Though metformin showed to have adverse events, still it results in very good therapeutic effects. It was reported that at the baseline, 40 patients had GI side effects due to metformin tablet which was reduced to 16 patients after switching to metformin capsule (Siavash *et al.*, 2017). Some studies have shown taking metformin tablets at mealtimes, or using careful dose adjustment to minimize poor compliance with the immediate-release form of metformin (Hostalek *et al.*, 2015) or switching to an extended-release form of metformin can reduce GI symptoms (Kim *et al.*, 2012; Jabbour *et al.*, 2011). Pernicious anemia caused by vitamin B12 deficiency was reported with patients taking metformin continuously for a long time (Filioussi *et al.*, 2003). Although metformin may improve weight loss regardless of diabetes, it may not confer long-term safety benefits. Metformin showed to induce complications in addition to the gastrointestinal effects, including pancreatitis, hepatitis, vitamin B12, and coagulation abnormalities, and reactive hypoglycemia (Shurab *et al.*, 2020). In this study, 16 cases were observed with lactic acidosis. However, the occurrence of this adverse event has been reported in clinical conditions seems very rare; less than 10 cases in every 100,000 patients (DeFronzo *et al.*, 2016). Metformin was associated with a lower or no significant difference in HbA1C levels compared with any of the other drug classes (Palmer *et al.*, 2016).

Conclusions

Metformin may produce different kinds of adverse events but still, it is one of the best drugs available for the treatment of diabetes. Lactic acidosis and hypoglycemia were found to be the most occurring adverse events that were associated with metformin. The drug could be formulated into capsules dosage form to reduce its risk. Cough, edema, lower back pain, rash were found to be less frequent but it could not be ignored from monitoring. The severity of adverse drug reactions was also found to be mild which implies that the drug is safer as compared to its risk.

Conflict of Interest

There is no conflict of Interest.

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