ORIGINAL ARTICLE

The Reported Adverse Events of Metformin: A Descriptive Analysis Using Data from VigiBase

Nehad Jaser Ahmad[1], Nahed I. Alobaidi[2], Bandar H. AlMatrafi[2], Ahmed D. Alonazi[2], Zahaa E. AlRashdi[2], Abdullah H. AlOnazi[2]

[1]Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia, [2]Department of Pharmacy, King Khaled Hospital and Prince Sultan Center for Health Care, Al-Kharj, Saudi Arabia

Abstract

Aim: Metformin is a well-established component of diabetes management. It is generally safe and well-tolerated but may cause several adverse events. The present study aimed to describe the reported adverse events of metformin. **Methods:** This was a descriptive analysis that was conducted using data from VigiBase to describe the reported adverse events of metformin use. **Results:** Till October 23, 2022, 100,993 metformin adverse event reports were submitted to the world health organization's global database (VigiBase). More than 57% of the patients were female and 42.49% of them were male. **Conclusions:** Gastrointestinal problems, abnormalities of metabolism and nutrition, general disorders, and conditions at the administration site were the most frequently reported side effects of metformin use. To reduce metformin adverse medication events, appropriate interventions such as targeted education should be implemented. Pharmacists should monitor their patients continuously to ensure the safe use of the medication.

Key words: Adverse events, metformin, reporting, VigiBase

INTRODUCTION

Diabetes mellitus, according to the World Health Organization, is a metabolic disease that is chronic and marked by high blood sugar levels. Over time, this condition causes damage to the heart, blood vessels, eyes, kidneys, and nerves. Type 2 diabetes mellitus, which is characterized by insufficient insulin secretion, tissue insulin resistance, and an insufficient compensatory insulin secretory response, accounts for about 90% of cases of diabetes mellitus.[1,2] As the illness worsens, insulin secretion becomes unable to keep glucose levels in balance, leading to hyperglycemia. Obesity or having a greater body fat percentage, primarily in the abdominal area, are the main characteristics of patients with type 2 diabetes mellitus.[3]

As monotherapy in the early stages of type 2 diabetes and as an adjunct therapy to almost every other antihyperglycemic drug on the market today, metformin is a well-established component of diabetes management. Metformin has remained effective despite having low potency and a long list of contraindications due to its well-known effects on glucose metabolism and, as more recent research has shown, its benefits on other cardiovascular risk factors.[4]

In general, metformin is thought to be safe and well-tolerated. Up to 30% of people using metformin experience gastrointestinal adverse symptoms, including diarrhea, nausea, and vomiting.[5] Chest pain, headache, diaphoresis, hypoglycemia, weakness, and rhinitis are less frequent symptoms that some people report. Long-term metformin use is linked to decreased vitamin B12 levels, which should be watched closely in patients with peripheral neuropathy or anemia.[6] Metformin has a black box warning for lactic acidosis. One in 30,000 patients will experience this dangerous but uncommon adverse event.[5]

Address for correspondence:
Nehad Jaser Ahmad, Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia.
E-mail: n.ahmed@psau.edu.sa.

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The unique world health organization global database of documented potential adverse drug reactions is called VigiBase. With over 30 million suspected adverse drug reaction reports reported since 1968, it is the world's largest database of its sort. With new reports received, it is updated continuously.[7] The present study aimed to describe the reported adverse events of metformin.

METHODOLOGY

Study design

The present study was a descriptive analysis that was conducted using data from VigiBase to describe the reported adverse events of metformin use. The study included the reports that were submitted to VigiBase before October 24, 2022. Metformin was selected because it has several adverse events and it has a black box warning for lactic acidosis.

Data collection

The collected data included the geographical distribution of the reports, the age of the patients who had an adverse event, the gender of the patients who had an adverse event, and the most reported adverse events of metformin use. The study did not require ethical approval because it included information freely available in the public domain.

Data analysis

The data were gathered as excel sheet files and the data were given as numbers and percentages. Each value's percentage is expressed as a number that reflects its fractional portion out of 100.

RESULTS

Till October 23, 2022, 100,993 metformin adverse event reports were submitted to the World Health Organization's global database (VigiBase). About 37.91% of the reports were submitted by Americas countries and 32.98% of the reports were submitted by Asian countries [Table 1].

Table 2 shows the gender of the patients who had an adverse event. More than 57% of the patients were female and 42.49% of them were male.

Table 3 shows the age of the patients who had an adverse event. The age of about 44.25% of the patients was between 45 and 64 years and the age of 25.39% of the patients was between 65 and 74 years.

Table 4 shows the most reported adverse events of metformin. The most reported adverse events were gastrointestinal disorders (21%), metabolism and nutrition disorders (14%), general disorders and administration site conditions (10%), investigations (8%), nervous system disorders (8%), and skin and subcutaneous tissue disorders (5%).

Table 1: The geographical distribution of the reports.

Continent	Number	Percentage
Africa	1533	1.52
Americas	38,287	37.91
Asia	33,311	32.98
Europe	26,534	26.27
Oceania	1328	1.31
Total	100,993	100.00

Table 2: The gender of the patients

Gender	Number	Percentage
Male	40,604	42.49
Female	54,959	57.51
Total	95,563	100.00

Table 3: The age of the patients

Age (years)	Number	Percentage
<2	189	0.24
2–11	131	0.17
12–17	461	0.58
18–44	9892	12.55
45–64	34,871	44.25
65–74	20,008	25.39
More than 74	13,247	16.81
Total	78,799	100.00

DISCUSSION

The present study showed that the most reported adverse events of metformin use were "gastrointestinal disorders," "metabolism and nutrition disorders," "general disorders and administration site conditions," "investigations, nervous system disorders," "skin and subcutaneous tissue disorders," "injury, poisoning, and procedural complications," and "renal and urinary disorders." The previous studies showed that metformin has no significant adverse effects; however, its use may result in a serious condition called lactic acidosis with several symptoms such as dizziness, muscle pain, severe drowsiness, tiredness, chills, fast/difficult breathing, blue/cold skin, stomach pain, slow/irregular heartbeat, diarrhea, vomiting, or nausea.[8-11] Moreover, Lalau and Scheen reported that gastrointestinal intolerance is one of the most common events, while lactic acidosis is uncommon but has substantial side effects.[12,13]Similar to our results, Nabrdalik

Table 4: The most reported adverse events of metformin

Adverse event	Number	Percentage
Gastrointestinal disorders	36,707	21
Metabolism and nutrition disorders	24,304	14
General disorders and administration site conditions	18,131	10
Investigations	14,660	8
Nervous system disorders	13,778	8
Skin and subcutaneous tissue disorders	9644	5
Injury, poisoning, and procedural complications	8591	5
Renal and urinary disorders	8254	5
Psychiatric disorders	6149	4
Respiratory, thoracic, and mediastinal disorders	4610	3
Musculoskeletal and connective tissue disorders	4448	3
Cardiac disorders	4201	2
Vascular disorders	3541	2
Infections and infestations	3124	2
Product issues	2982	2

et al. stated that compared to other antidiabetic medications, type 2 diabetes patients on metformin have an increased risk of experiencing gastrointestinal side effects including nausea, diarrhea, and stomach pain.[14] Furthermore, Sanchez-Rangel and Inzucchi reported that the most common side effects of metformin are gastrointestinal in nature including nausea, diarrhea, and abdominal discomfort.[15]

The most often reported side effects of metformin, according to Rojas *et al.*, were headaches, nausea, vomiting, diarrhea, and stomach pain.[16] Similar to our results, Bouchoucha *et al* stated that the main side effects of metformin are gastrointestinal intolerance, which includes anorexia, abdominal pain, diarrhea, nausea, and vomiting. They also reported that about 30% of patients experience gastrointestinal side effects, which have caused 5%–10% of patients to stop receiving treatment.[17] Furthermore, Ji *et al.* reported that only half of the Chinese patients with type 2 diabetes take metformin, possibly due to concerns about gastrointestinal side effects and renal insufficiency.[18] Kirpichnikov *et al.* reported that the most common side effects of metformin are nausea, abdominal discomfort, and diarrhea and that 20–30% of the patients had at least one of these side effects.[19]

The present study showed also that nervous system disorders were a common adverse effects of metformin use. The previous studies have found low vitamin B12 levels in patients taking metformin and that the major concern with this adverse event is its possible association with irreversible neurological consequences.[15,20] According to Bauman et al, 10–30% of metformin-treated individuals have indications of decreased vitamin B12 absorption as a result of calcium-dependent ileal membrane antagonism, an effect that can be restored with calcium supplements.[21] Aroda *et al.* stated that low levels of vitamin B12 could potentially lead to an increased occurrence of peripheral neuropathy.[20]

CONCLUSION

Gastrointestinal problems, abnormalities of metabolism and nutrition, general disorders, and conditions at the administration site were the most frequently reported side effects of metformin use. To reduce metformin adverse medication events, appropriate interventions such as targeted education for the health-care providers and for the patients should be implemented. Moreover, pharmacists should monitor their patients continuously to ensure the safe use of the medication.

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