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PHARMACOLOGY

PREVALENCE OF METFORMIN-INDUCED GASTROINTESTINAL PROBLEMS

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Abstract: Metformin is used as an anti-diabetic medicine among oral hypoglycemic drugs, which produces many gastrointestinal problems. This study aims to investigate the effect of metformin-induced gastrointestinal problems and its prevalence. The cross-sectional study design was adopted using a convenience sampling technique, at different Diabetic Centers of Lahore and Faisalabad, Pakistan from, June-2017 to November-2017. A total of 300 male and female patients participated in the study between 26 to 85 years and diagnosed with type-II diabetes. Data were directly collected from the patients and the prevalence of metformin-induced gastrointestinal intolerance was determined by the symptoms of the patients. Data were analyzed using SPSS version 21. Results showed a significant difference between gender and symptoms ($p = 0.029$). Moreover, gastrointestinal problems were found to be dose-related. A significant difference existed between patients taking 500 mg and those taking 850 mg of metformin ($p = 0.006$), patients who were taking 500 mg and those taking 1000 mg of metformin ($p = 0.000$) and patients on 850 mg with those taking 1000 mg of metformin ($p = 0.022$). The prevalence of metformin-induced gastrointestinal symptoms was 45.8%. Most commonly occurring symptoms were, constipation (41.35%) followed by dyspepsia (27.89%), abdominal pain (26.92%), bloating and heartburn (25%), indigestion (15.38%), anorexia (11.54%), diarrhea (6.58%), flatulence (7.69%), nausea (6.73%) and vomiting (2.88%). It was concluded that gastrointestinal intolerance was more in females as compared to males. The gastrointestinal problems increased with the increase in dose. The side effects were irrespective of the age and the most common gastrointestinal symptom was found to be constipation.

Keywords: metformin, gastrointestinal, diabetes

Diabetes is characterized by hyperglycemia. Type II diabetes is a health problem worldwide. It is affecting more than 415 million people and by the end of 2040, this figure is expected to reach 642 million. Over the last few decenniums the prevalence of diabetes has amplified along with, obesity. Another study shows that in most developed countries diabetes is the 4th major cause of death. World Health Organization (WHO) reported that 12.9 million persons (10 percent of the population) of Pakistan are diabetics; 9.4 million patients suffering from diabetes are diagnosed and 3.5 million are undiagnosed. Furthermore, people having pre-diabetes are 38 million (women 20.5 percent and men 15.9 percent). Because of diabetes and its complications 120,000 people die in Pakistan every year (1). The options in the treatment are diet, oral antihyperglycemic drugs (OHD), and insulin (2). Metformin is used as an anti-diabetic drug among OHDs. In addition to reducing the oxidation of the fatty acids, it reduces the hepatic production of glucose and its intestinal absorption. Moreover, it causes an increase in insulin sensitivity, thereby reducing the resistance of insulin that is often a problem in type-II diabetes patients (3).

However, like all other drugs, metformin produces many GIT problems. The most common GI symptoms are flatulence, constipation, dyspepsia, diarrhea, heartburn, nausea, abdominal pain, bloating and retching (4). Metformin causes GI intolerance in 20–30% of patients which leads to the poor standard of life and treatment adherence in diabetic patients (5). It has been found that about 5% of patients cannot tolerate the treatment due to gastrointestinal side effects (6).

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The main mechanism lying under the metformin-induced GI intolerance is not clear. However, different hypotheses have been suggested which include stimulation of release of serotonin in the intestine, malabsorption of bile salts and alteration in incretin as well as the metabolism of glucose. The release of serotonin from the intestine is responsible for the GI symptoms such as nausea, vomiting and diarrhea which are similar to metformin intolerance (7). A recent study has reported phenotypic and genetic determinants of severe intolerance of metformin in Type-II diabetic individuals (8). The aims and objectives of the present study are to investigate the prevalence of metformin-induced GIT problems.

EXPERIMENTAL

The cross-sectional study design was adopted using a convenience sampling technique. A total of 300 patients participated in the study. The study was conducted at Allied Hospital Faisalabad, Faisalabad Diabetic Center and Diabetic Institute Pakistan Lahore from June 2017 to November 2017.

During the study, both genders, between the age range from 26 to 85 years, diagnosed with type-II diabetes were included. Patients using metformin as an anti-diabetic drug were considered. Patients of having age less than 26 and greater than 85 were excluded in the study. Patients taking insulin were also excluded.

Data collection procedure

Data were collected from the patients by visiting the outpatient departments of different government and private hospitals. In this study, patients having type-II diabetes using metformin of different doses (500 mg, 850 mg and 1000 mg) were considered. Patients having symptoms of metformin-induced gastrointestinal problems were noted. The gastrointestinal symptoms induced by metformin were linked with age, dose and gender. A proforma was filled by the patient giving his/her consent, in the presence of a physician or a diabetologist. The demographic data (name, age, gender, phone number), metformin usage, presence of symptoms and presence of any other disease were collected directly from the patient and patient's record file.

Ethical considerations

The study was approved by Advance Studies Research Board, Lahore College for Women University Lahore Pakistan. All the ethical considerations were taken into account. Afterward, the written permission from the concerned authorities of the relevant hospitals and diabetic centers was taken. The research protocol and the Proforma along with consent form (both in English and Urdu) were also approved by the ethical committee of the respective hospitals. The consent of the participants was taken and confidentiality of information was assured.

Table 1. Demographic characteristics of patients.

Age (years) group	Frequency	Percentage %	M	S D	p-value
26-40	35	15.4	1.23	1.416	0.299
41-55	132	58.1	0.83	1.095	
56-70	53	23.3	1.02	1.232	
71-85	7	3.1	1.14	1.464	

Table 2. Presence of symptoms with respect to gender.

Gender	N	M	S.D	df	t-value	p-value
Male	77	0.70	1.065	225	-2.201	0.029
Female	150	1.07	1.241			

Table 3. Comparison between 500 mg and 850 mg dose of metformin on symptoms.

Dose	N	M	S.D	df	t-value	p-value
500 mg	141	0.54	0.945	164	-2.784	0.006
850 mg	25	1.12	1.054			

Table 4. Comparison between 500 mg and 1000 mg dose of metformin on symptoms.

Dose	N	M	S.D	df	t-value	p-value
500 mg	141	0.54	0.945	200	-7.749	0.000
1000 mg	61	1.80	1.302			

Table 5. Comparison between 850 mg and 1000 mg dose of metformin on symptoms.

Dose	N	M	S.D	df	t-value	p-value
850mg	25	1.12	1.054	84	-2.328	0.022
1000mg	61	1.80	1.302			

Table 6. Prevalence of metformin-induced GIT symptoms.

Symptoms	No. of patients	Symptom percentage
Constipation	43	41.35%
Dyspepsia	29	27.89%
Abdominal pain	28	26.92%
Bloating	26	25%
Heartburn	26	25%
Indigestion	16	15.38%
Anorexia	12	11.54%
Diarrhea	11	10.58%
Flatulence	8	7.69%
Nausea	7	6.73%
Vomiting	3	2.88%

Statistical analysis

For statistical analysis statistical package for science version- 21 (SPSS-21) was used. Descriptive statistics were used for frequencies and percentages. Independent sample T-test was used to check the difference between age groups, dose and gender. P-value equal to 0.05 was taken as significant.

RESULTS

Demographic characteristics of patients

The demographic characteristics of patients are depicted in Table 1. The age ranges from 26 to 85 years. Study participants were grouped into four age groups. The first age group was 26-40 numbering 35 (15.4%). The second group was of 41-55 years. The participants of this age group were 132 (58.1%) The third age group was of 56-70 years, having 53 participants (23.3%). The fourth group was 71-85 years and the total participants of this group were 7 (3.1%). Results showed an insignificant difference among different symptoms of diabetic patients in different age groups. This analysis showed that there was no difference in terms of their symptoms in different age groups. Also, it was noted that whether the participant was at the age of 26 years or the age of 85 years, they experienced the same symptoms of metformin drug. Patients developing GIT symptoms after taking metformin were included in the study. Patients with GIT symptoms have no additional (extra) gastrointestinal disorders.

Presence of symptoms with respect to gender

The presence of symptoms with respect to gender is depicted in Table 2. Results showed that a significant difference exists between males and females on exposure of symptoms ($p = 0.029$). It also shows that females experienced more symptoms as compared to males.

Comparison between 500 mg and 850 mg dose of metformin on symptoms

Table 3 shows that a significant difference exists between patients who were taking 500 mg

dose and those taking 850 mg dose of metformin (p = 0.006). Results further showed that those patients who were taking 850 mg dose of the drug were facing more GIT problems as compared to those who were taking 500 mg.

Comparison between 500 mg and 1000 mg dose of metformin on symptoms

Table 4 shows that there was a significant difference between those patients who were taking 500 mg dose of metformin and those patients who were taking 1000 mg dose of metformin (p = 0.000). Additionally, results showed that the patients taking 1000 mg dose of drug faced more GIT problems than those patients who were taking 500 mg.

Comparison between 850 mg and 1000 mg dose of metformin on symptoms

Table 5 shows that a significant difference exists between the symptoms of patients taking 850 mg of metformin and patients who were taking 1000 mg dose of metformin (p = 0.022). Those patients who were taking 1000 mg dose faced more GIT problems as compared to those patients who were taking 850 mg dose of the drug.

Prevalence of metformin induced GIT symptoms

Table 6 shows the prevalence of symptoms in diabetic patients taking metformin. Results showed that the most commonly occurring symptom was constipation with 41.35%. It also showed that the other symptoms occurring with the use of metformin were dyspepsia (27.89%), abdominal pain (26.92%), bloating and heartburn (25%), indigestion (15.38%), anorexia (11.54%), diarrhea (6.58%), flatulence (7.69%), nausea (6.73%) and vomiting (2.88%).

Presence of symptoms

Results showed that 45.8% of the participants experienced symptoms while 54.2% were free of any symptoms.

DISCUSSION AND CONCLUSION

The study was conducted to investigate the prevalence of metformin-induced GIT problems. The study findings showed that females experience more symptoms as compared to males. This is in line with the previous study (9).

Furthermore, the study findings depicted that those patients who were taking 500 mg of metformin experienced less gastrointestinal symptoms than those who were taking 850 mg or 1000 mg of the drug. Similarly, patients taking a dose 850 mg of metformin experienced less symptoms compared to those taking 1000 mg of the drug. This showed that as the dose of the drug increased, the gastrointestinal symptoms augmented. These findings are consistent with the previous studies (6, 10-11). However, Dandona's (1983) findings were contradictory which reported that gastrointestinal adverse effects were not dependent on the dose of metformin. He determined that the patients on different doses of metformin were observed and results depicted that the rate or severity of gastrointestinal intolerance was irrespective of the dose of the drug (12).

Metformin causes a gastrointestinal disturbance. These side effects include constipation, dyspepsia, abdominal pain, bloating, indigestion, heartburn, anorexia, diarrhea, flatulence, nausea and vomiting. This was consistent with the previous studies (13, 17).

In the present study, the most commonly occurring adverse effect was constipation and the least common symptom was vomiting. Whereas Bouchoucha et al., (14) found that diarrhea and vomiting were the most commonly occurring symptoms. Additionally, present study findings showed a prevalence of other GI symptoms that is, dyspepsia, abdominal pain, bloating, heartburn, indigestion, anorexia, flatulence, and nausea. Burton and his fellows (4) found GI symptoms were diarrhea followed by heartburn, and nausea, abdominal pain, bloating, and retching.

About 45.8% of the patients reported either single or multiple GI symptoms. Cubeddu and his coworkers (15) investigated that about 30% of patients taking metformin experienced GI side effects. Whereas Burton et al., (4) showed that about 88% of individuals reported either single or multiple GI symptoms in diabetic patients. Haupt et al., (16) found that gastrointestinal side effects appeared in about 7% of patients mainly in at start of the treatment which disappeared as therapy continued but present study findings showed that the symptoms were consistently present with the metformin. This is consistent with the findings of Foss and Clemet (17) in which patients experienced these GI symptoms even after several years of stable metformin therapy.

Moreover, the study showed that metformin-induced gastrointestinal symptoms occurred irrespective of the age. This result is consistent with a study conducted by Jones (18) and his fellows who investigated that in pediatric patients having type-II diabetes, taking metformin, experienced gastrointestinal symptoms. The adverse events experienced

by these individuals were consistent with adverse events reported for adults. Diarrhea and abdominal pain were observed in these metformin-treated participants. These findings are consistent with Schweizer et al. (19) and Josephkutty (20), where gastrointestinal side effects also occurred in elderly patients.

It was concluded that GIT intolerance was more in females as compared to males. In addition, metformin-induced GI disturbance was not associated with the age group. The study depicted that the GI problems increased with the increase in the dose of metformin. The most common GI symptom found was constipation and the least common was vomiting.

Conflict of interest

The authors declare no conflicts of interest.

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