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THE COMPLICATIONS AND OUTCOMES OF ORAL ANTIDIABETIC DRUG POISONING IN PATIENTS HOSPITALIZED AT RAZI HOSPITAL, 2005-2012

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ABSTRACT

Background: Oral antidiabetic drug poisoning has been increased due to the greater access to drug treatment and high prevalence of diabetes worldwide. Glibenclamide and metformin poisoning can cause hypoglycemia and acidosis resistant to therapy, respectively. Since these two side effects, in addition to other complications of oral antidiabetic drug poisoning can be potentially life threatening, so we decided to investigate the frequency of such side effects following the metformin and glibenclamide poisoning. **Materials and methods:** This case series was conducted on all patient admitted to Razi Hospital due to the metformin and glibenclamide poisoning during the years 2005-2012. Patients' medical records were collected including the basic demographic information, types of prescription drugs and their medicine causes, clinical manifestations, characteristics of hospitalized unit, duration of hospitalization, type of therapy and their outcome. **Results:** One hundred thirty-two poisoned patients entered the study with a mean age of 36.4 ± 10.70 (15 to 73 years). Lethargy, fatigue and weakness are the most common early signs of our poisoned patients with metformin (57.14%), followed by gastrointestinal symptoms such as abdominal pain (40%), nausea and vomiting (14.2%) and tremor (14.2%). Glibenclamide overdose generally led to neuroglycopenic symptoms including weakness and tremor in 91.7% and 64.9% of overall patients, respectively. The

remains mostly had lethargy and drowsiness (33.3%), nausea and vomiting (33%), seizures (16%), abdominal pain (11.3%) and coma (8.24%). In addition to general supportive care, dextrose injection, bicarbonate and hemodialysis were used for the patients with hypoglycemia and metformin poisoning patients. All the patients survived were with not long-term complication and end organs failure. **Conclusion:** Our finding suggested that suitable and timely management of poisoned patients with glibenclamide and metformin might lead to better outcomes in such cases.

KEYWORDS: glibenclamide, metformin, poisoning, Ahvaz

INTRODUCTION

Glibenclamide and metformin are two common anti-hyperglycemic agents, available on the market. Metformin as a biguanide is widely used in the treatment of diabetes mellitus and some specific conditions such as polycystic ovary syndrome (PCOS). Despite the favorable safety profile that has been demonstrated over the past 50 years of clinical experience, metformin is associated with side effects in the form of diarrhea, abdominal pain, nausea, vomiting and headache.[1] Metformin-associated lactic acidosis (MALA) is a serious complication, occurs following the metformin accumulation or its massive overdose due to inhibition of mitochondrial glycerophosphate dehydrogenase and ultimately inhibition of gluconeogenesis or the mitochondrial respiratory chain complex.[2, 3] Although the prevalence of MALA is very rare (less than 10 cases per 100,000), but resulted in the deaths of 30-50% of the patients.[4] Three hundred cases of intentional metformin overdose, with a total of 9 deaths have been reported by American Association of Poison Control Centers in the year 2006.[5] The standard dose of metformin can rarely cause toxicity; however, it is contraindicated in elderly patients with hepatorenal failure and patients with cardiovascular problems, such as congestive heart failure.[4]

Glibenclamide, also known as glyburide, is a second-generation sulfonylureas, which triggers the opening of calcium channel and subsequently stimulation of pancreatic insulin secretion through the direct connection with ATP-sensitive potassium channel.[6] This mechanism of drug action leads to decreased level of blood glucose in patients with diabetes.[7] Although the maximum daily dose of glibenclamide is 200 mg /day, but the therapy usually begins with a low dose of 2.5 to 5.0 mg per day. The administered drug absorbed in a one-hour period, and reaches its peak value within 4 hours. A half-life of 10 hours is reported throughout the body and the drug is eliminated from the plasma for nearly 24 hours, so the anti-

hyperglycemic effects remains for up to 24 hours following the first administration.[8] In considering these issues, hypoglycemia (glucose levels below 60 mg/dL) is known to be the most common adverse effect attributed to glibenclamide. The annual incidence rate of sulfonylurea-induced hypoglycemia is approximately 1-2 % among treated patients, in which is a leading cause of death or permanent neurological deficits in more than 10% and 5% of all cases, respectively.[9]

Considering the risk of these drug toxicities from both therapeutic dosing and intentional overdose, identification of clinical and laboratory signs, as well as early symptoms of poisoning can lead to improvement approaches in the field of appropriate diagnosis and therapy. Therefore, this study was aimed to assess the medical records of poising cases with metformin and glibenclamide.

MATERIALS AND METHODS

In this case-series study, the medical records of all poisoned patients hospitalized in Razi Hospital due to metformin and glibenclamide toxicity was evaluated during the years 2005-2012. A questionnaire was used to collect data on basic demographic information (age, sex, marital status and citizenship), types of prescription drugs and their medicine causes, clinical manifestations, characteristics of hospitalized unit (general wards or ICU), duration of hospitalization, type of therapy and their outcome. Patients taking metformin and glibenclamide were classified as Group 1 and 2, respectively. Our study group consisted of patients who had been referred to the hospital due to acute poisoning. Therefore, patients with underlying end organ failure, poisoned cases associated with chronic complications of such drugs as well as those with possible multiple drug intake were excluded from the study. Patients' demographic characteristics and descriptive indicators of the studied variables were analyzed, using SPSS Software ver. 19.

RESULTS

One hundred thirty-two poisoned patients entered the study with a mean age of 36.4 ± 10.70 (15 to 73 years), consist of 81 women and 51 men. Those who were 30–40 years of age are considered to be in the most commonly exposed age groups in both sexes (30.34%), while the drug toxicity rate was low in patients over 60 years of age (4%). Diabetes mellitus type 2 and PCOS were the most common underlying diseases found in 26.4% and 11% of poisoned patients, respectively. Thirty-five patients were poisoned with metformin (26%) and 97 cases were poisoned with glibenclamide (74%). All the poisoned patients assessed in our study had

suicidal thoughts at some point (Table 1). The average dosage among metformin-poisoned (54%) and glibenclamide-poisoned (65%) cases were 25,000 mg (range from 5,000 to 60,000 mg) and 70 mg (range from 25 to 120 mg), respectively. The average onset of poisoning symptom related to glibenclamide overdose was 7 hours and the metformin overdose was 8 hours.

Table 1. The clinical condition of patients poisoned with glibenclamide and metformin

Variables		**Metformin (35)**	**Glybenclamide(97)**
Gender		22 F, 13 M	59 F, 38 M
Age		30 (15-70)	48.7(22-73)
Clinical Presentations	Nausea and vomiting	(14.2)5	32(33)
	Abdominal pain	14(40)	11(11.3)
	Hypoglycemia	5(14.2)	89(91.7)
	Lethargy and drowsiness	20(57.14)	32(33.3)
	Weakness	20(57.14)	89(91.7)
	Tremor	5(14.2)	63(64.9)
	Seizure	0	15(16)
	Coma	2(5.71)	8(8.24)
Hospitalized Unit	General ward	31(85.6)	34(35)
	ICU	7(20)	89(91.7)
Treatment	Bicarbonate	4(11.4)	-
	Activated charcoal	35(100)	97(100)
	Hemodialysis	5(14.2)	-
	Dextrose	5(14.2)	89(91.7)

Lethargy, fatigue and weakness are the most common early signs of our poisoned patients with metformin (57.14%), followed by gastrointestinal symptoms such as abdominal pain (40%), nausea and vomiting (14.2%) and tremor (14.2%). In most cases (90%), mild to moderate symptoms were observed at doses higher than 2500 g and severe symptoms were seen in higher dose of drug toxicity (more than 5000 g). Glibenclamide overdose generally led to neuroglycopenic symptoms including weakness and tremor in 91.7% and 64.9% of overall patients, respectively. The remains mostly had lethargy and drowsiness (33.3%), nausea and vomiting (33%), seizures (16%), abdominal pain (11.3%) and coma (8.24%). Hypoglycemia was reported in 91.7% and 14.2% of poisoned patients with glibenclamide and metformin. Mild to moderate symptoms were almost observed at all doses more than 50 mg per day, while severe symptoms such as coma were observed at doses above 95 mg. Only 80 mg dose of toxicity led to coma in one patient. Eighty-nine patients with glibenclamide poisoning and seven cases of metformin overdoses hospitalized in ICU due to hypoglycemia

and acidosis resistant to therapy (Table 1). There were no significant correlation between age, sex and the duration of hospitalization ($P<0.05$).

Therapeutic interventions including the activated charcoal was used to treat all the poisoned patients. Bicarbonate and dextrose were administered for patients with acidosis and hypoglycemia, respectively. Furthermore, those with sustained severe acidosis were undergoing hemodialysis. All the therapeutic interventions were done on time and all the survived patients had no sign of neurological involvement during hospital discharge.

DISCUSSION

Sulfonylureas and biguanides are the most common medications used to treat diabetes. Drug overdose-related symptoms vary widely, but the hypoglycemia and the lactic acidosis are the most severe side effects, which can be fatal or cause permanent neurological deficit within patients. We examined 135 poisoned patients caused by metformin and glibenclamide overdose during an 8-year period. Although the overdose of such drugs can occur within the normal dose range, but all the poisoned patients assessed in our study had suicidal thoughts at some point.

Lethargy, fatigue and weakness are the most common early signs of our poisoned patients with metformin (57.14%), followed by gastrointestinal symptoms such as abdominal pain (40%) and, nausea and vomiting (14.2%). Glibenclamide overdose generally led to neuroglycopenic symptoms including weakness and tremor in 91.7% and 64.9% of overall patients, respectively. Various studies showed different results in terms of drug overdose symptoms. According to Behnoosh et al. (10), weakness and dizziness were the most common symptoms following metformin and glibenclamide poisoning, while other studies found the symptoms nausea, diarrhea and dizziness as the most frequently side effects experienced following the metformin toxicity [11, 12]. According to Dalan et al.[13], loss of consciousness (40%), dizziness (33%), seizures (27%) and coma (6.7%) were the most frequently encountered symptoms in patients with glibenclamide overdose.

In our study, the frequency of seizures and coma were 16% and 8.24% in total poisoning cases with glibenclamide, and all the survived patients had no symptoms of neurological involvement during the hospital discharge. Based on a large survey by Von Mach et al. [14], only the 13.4% and 14.4% of poisoned patients with biguanides and sulfonylureas have shown severe complications of toxicity, respectively. Furthermore, Shadnia et al.[15] reported

two cases of death out of the 204 poisoned patients with metformin, who were taking other medication with anti-hyperglycemic agent. It seems that metformin overdose is generally lead to altered level of consciousness in addition to digestive problems, while neurological disorders are more common among glibenclamide-poisoned patients. Average daily dose of metformin was 2.5 mg/day in our study, while in Shadnia et al. and McNamara et al. were 15 mg/day and 10 mg/day.[15,16] Therefore, the differences between our findings and the previous studies might be due to drug dosage.

More than 70%-poisoned patients with described drugs had the onset of clinical symptoms in less than 7 hours. Nearly 20% of metformin poisoned patients hospitalized in ICU and the remains hospitalized in general wards, as 63% of them were discharged within two days. However, 91.7% of glibenclamide poisoned patients hospitalized in ICU and 75% of them had over two-day hospitalization requirement. Metformin is uptake into the intestine relatively quickly and approximately 90% of absorbed drug is eliminated through glomerular filtration and tubular secretion in unmetabolized form, so that the metformin half-life is 6.5 hours among individuals with normal renal function.[17] However, the half-life of glibenclamide is nearly 10 hours and is remained in the body for up to 24 hours.[8] These findings suggested that the glibenclamide overdoses is more likely to accumulate than metformin, which may explain the differences between symptoms of poisoning with such drugs.

All the intoxicated patients had a suicide attempts at some point. Mean age of studied patients was 36.4 ± 10.70 (15 to 73 years), consist of 97 women and 38 men. These findings is in parallel with other studies, as the average age of Behnoosh et al. and Shadnia et al. patients were 30.8 and 26.3 years, respectively. Furthermore, women were the dominant patient population in such surveys, same to us (10, 15). According to Avci et al. study on suicide commitment with metformin, 60% of poisoned patients were female and the average age of the cases was 22 years [18]. Malakouti et al. study conducted in Iran revealed the higher rate of suicide among women than men in some regions and drug use was the prevalent means of suicide in such cases.[19]

Although the clinical symptoms of poisoned patients with glibenclamide and metformin were relatively similar, but hypoglycemia was an important distinction, currently being considered in the field of diagnosis of drug poisoning and may somehow accelerate the urgent medical care and ultimately improve patient outcomes. Lack of drug monitoring and evaluation of

laboratory tests were the main limitations of our study, while a relatively large sample size was the strengths of this study.

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