

## Determining the complications, mortality, and treatment of patients hospitalized at Baharloo hospital due to oral hypoglycemic drugs toxicity in 2008-9

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### ABSTRACT

**Background:** Glybenclamide and metformin are two of the most common oral hypoglycemic drugs which are often used in treatment of type II diabetes mellitus. Toxicity due to these drugs may occur intentionally, accidentally, or even at the normal dosage because of the progression of such internal diseases as renal dysfunction.

**Methods:** In this case series study, 59 patients poisoned with oral hypoglycemic agents referring to Baharloo Hospital were evaluated between March 2009 and September 2010.

**Results:** The most common clinical findings were lethargy (66.7%) and drowsiness (66.7%) that were mostly observed in patients who had concomitantly ingested glybenclamide and metformin. Metabolic acidosis was observed in 33.3% of the patients who had ingested metformin alone and 22.2 % of the patients who had ingested metformin together with glybenclamide. Some degrees of hypoglycemia were observed in 50.8% of the patients upon admission; nevertheless, severe hypoglycemia was seen only in 17% of them. The majority of the patients got improved within 3 days of hospitalization and got discharged. Although due to the severity of toxicity and its associated complications, 22.8% of the patients needed more than 3 days of hospitalization, permanent neurological complications and mortality did not happen to any of the patients.

**Conclusion:** Glybenclamide overdose leads to hypoglycemia and it can be prevented by careful monitoring of blood glucose and immediate treatment with intravenous dextrose, mostly occurring due to its hypoglycemic effects on the brain.

**Keywords:** Glybenclamide, metformin, oral hypoglycemic drugs, suicide, toxicity

### INTRODUCTION

Diabetes mellitus is a metabolic disorder that occurs due to deficiency in insulin secretion or insulin action. The incidence rate of this disease is 7.8%. Diabetes mellitus is generally divided into type I (insulin-dependent diabetes mellitus) and type II (non-insulin-dependent diabetes mellitus). All type I diabetic patients depend on insulin in their treatment; however, type I diabetic patients can use oral drugs in place of insulin. At present, five different categories of oral anti-diabetes drugs are available which are listed below:

- a) biguanides
- b) sulfonylureas
- 3) thiazolidines

- 4) alpha glucosidase inhibitors
- 5- meglitinides

Insulin and sulfonylurea overdose result in hypoglycemia. In overdose with long-term effect drugs, such as *chlorpropamide*, hypoglycemia may last for several days. Hypoglycemic toxicity with metformin which belongs to the category of biguanides is a lot less common than with sulfonylurea. Metformin; on the other hand, can cause severe lactic acidosis which is fatal in 50% of the cases (2).

Disorder in the level of consciousness is the most common symptom of sulfonylurea overdose which may not respond to treatment

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with glucose desirably. In sulfonylurea overdose, treatment is done with glucose, glucagon, diazoxide, and acterotides. The concomitant use of these drugs with *salicylate*, sulfonylurea, and monoamine oxidase and clofibrate enzymes can precipitate hypoglycemia.

Metformin is a biguanide which is currently used as a proper alternative for oral hypoglycemic drugs such as sulfonylurea. Biguanides can lead to hypoglycemia only when used concomitantly with ethanol or other hypoglycemic drugs or in the case of severe hepatic dysfunction. All biguanides bring about lactic acidosis but this complication is more common in the case of fenformin. Renal dysfunction may provide the proper grounds for progression towards lactic acidosis. Morbidity and mortality due to toxicity with biguanides usually occurs following lactic acidosis.

The incidence of mortality and morbidity is more in elderly and patients with renal dysfunction and other internal diseases, and death may ever occur after bicarbonate and acidosis correction (3). The use of thiazolidine and alpha glucosidase enzyme inhibitors in acute overdose has fewer complications but acarbose and all thiazolidines in chronic usage lead to liver damage which necessitates the discontinuation of the drug and supportive care.

This study was done to identify the complications and mortality and morbidity rate due to toxicity with hypoglycemic drugs overdose, since poisoning with such drugs, that may even incidentally occur in diabetic patients, is one such toxicity that its early diagnosis and treatment can play an important role in lowering the mortality and morbidity rate and decreasing its paralyzing complications, such as irreversible damage to the nervous system.

## MATERIALS AND METHODS

In this study, of all patients referring to the poisoning emergency ward of Baharloo Hospital between March 2009 and September 2010, 59 patients diagnosed with oral hypoglycemic drugs were evaluated.

Demographic data and data on complications due to hypoglycemic agents were obtained from the patients' profiles which had been recorded by physicians.

## RESULTS

In this study, 59 patients, 81.4% female and 18.6 % male, were evaluated. The mean age for female subjects was  $30.85 \pm 13.07$  ranging in age from 13 to 60, while the mean age for male subjects was  $38 \pm 20.25$  ranging in age from 16 to 70. The mean of age for all subjects was  $32 \pm 14.73$ . The most common age for the incidence of poisoning with oral hypoglycemic drugs was 30 so that 20.3% of the patients were under 20 and 33.9% of them were between 20 and 29. The lowest rate was for the patients between 50 and 59-year old patients so that only 6.8% of the patients were in this range.

In this study, 35 patients had used glybenclamide alone. The most common clinical symptoms were lethargy and drowsiness that were observed in 51.4% of the patients. Trydopomile was the least common complication which only existed in 8.6% of the patients. Also, only 15 patients had used metformin that presented lethargy and drowsiness as their most common clinical symptoms (66.7%). This complication was seen in all patients who had used more than 25g metformin.

Decreased level of consciousness (GCS<15) was the rarest complication which developed in only 13.3% of the patients that quite unexpectedly had used less than 5g metformin. In this study, 9 patients had used metformin and glybenclamide together and their most common clinical symptom was the decreased level of consciousness (GCS<13) which was present in all of them. The other common symptoms were drowsiness and lethargy which were present in 66.7% of these patients; however, trydopomile was the rarest symptom which was only reported in one patient.

In examination of arterial blood gases, no abnormality was reported in 79.7% of the patients upon admission. Metabolic acidosis (PH lower than 7.35 accompanied with

carbonate drop and PCO<sub>2</sub> compensatory decreases) was observed in 333.3% of the patients who had used metformin.

Additionally, this complication was reported in 22.2% of the patients who had used metformin and glybenclamide concomitantly and in 5.7% of the patients who had only used glybenclamide. Overall, metabolic acidosis was observed in 15.3% of the patients. Respiratory acidosis (PH<7.35 accompanied with PCO<sub>2</sub> increase and bicarbonate compensatory increases) was only seen in only 8.6% of the patients who had used glybenclamide, and none of the patients who had used metformin alone or together with glybenclamide presented this complication.

In considering the development of lactic acidosis in the patients, noticing the difficulty in measuring cholera ion and lactate, a definitive conclusion could not be reached. Yet, with respect to the incidence of metabolic acidosis in 7 patients who had used metformin alone or together with glybenclamide, the incidence of lactate acidosis seems to be 11.86%. Nearly half of the patients had degrees of hypoglycemia upon admission so that 50.9%

of the patients had primary blood glucose levels lower than 70mg/dl.

Of these patients, 10.2% had primary blood glucose level between 60 and 70 and 23.7% had primary blood glucose levels between 50 and 60. Primary blood glucose level lower than 50 was only seen in 17% of the patients while levels lower than 70 were not seen in any of the patients who had used metformin alone.

Minimum blood glucose levels during treatment were measured on 4 hour intervals. In 32.2% of the patients, the minimum blood glucose levels which were measured in four hour intervals during the treatment time were reported to have, at least once, decreased to less than 70. Of these, only 10.2% had levels below 50mg/dl and 18.6% had levels between 50 and 60 mg/dl.

Tables 1 and 2 show the frequency of primary blood glucose and treatment blood glucose levels based on the type of drugs.

**Table 1:** Frequency of primery suger blood of patients in time of admitting base on kind of used drugs

Drug Primry blood suger	Glybenclamide	Metformine	Both	Total
30-40	3(8.6)	0	0	3(5.1)
40-50	6(17.1)	0	1(11.1)	7(11.9)
50-60	13(37.1)	0	1(11.1)	14(23.7)
60-70	6(17.1)	0	0	6(10.2)
70-100	1(2.9)	3(20)	0	4(6.8)
>100	6(17.1)	12(80)	7(77.8)	25(42.4)

**Table 2:** Frequency of primery suger blood of patients during treatment, base on kind of used drugs

Drug Blood suger luring treatment	Glybenclamide	Metformine	Both	Total
30-40	2(5.7)	0	0	2(3.4)
40-50	3(8.6)	0	1(11.1)	4(6.8)
50-60	8(22.9)	1(6.7)	2(22.2)	11(18.6)
60-70	2(5.7)	0	0	2(3.4)
70-100	15(42.9)	8(53.3)	0	23(39)
>100	5(14.3)	6(40)	6(66.7)	17(28.8)

In terms of the motivation for using oral hypoglycemic drugs, 93.2% of the patients had used these drugs for committing suicide. The greatest incidence of the intentional abuse of these drugs occurred in patients under 30 years of age in a way that 34.9% of the patients were 20 to 29 years old and 20.3% of them were under 20. Also, the incidental usage of these drugs happened in only four patients (6.8%) who were 30 to 59 years old.

In terms of treatment, 69.5% of the patients that had been treated due to oral hypoglycemic drugs overdose were discharged after complete recovery. Also, 30.5% of these patients, despite the need for further treatment and hospitalization, were discharged with their own consent. Nevertheless, severe complications due to toxicity, such as irreversible neurologic complications and morbidity and mortality, were not observed in any of the patients.

## DISCUSSION

The patients who are hospitalized due to poisoning with oral hypoglycemic drugs at Baharloo Hospital, one of the most specialized centers for poisoning and toxicity, are young in terms of age distribution (mean age=32.19±14.73). In Von Mach's study (5) which was conducted on 263 cases of poisoning with sulfonylurea, the patients' mean of age was 39.1 years. The mean of age in 172 cases of toxicity with beguanides in the same study was shown to be 44.6 years. It seems that the incidence of toxicity with oral hypoglycemic drugs in our patients, with a greater incidence, has been suicidal and has occurred at lower ages. Noticing the fact that youth form a great percentage of population of Iran, these figures are quite significant.

Notwithstanding, statistics from AAPCC indicate that the number of poisoning cases with oral hypoglycemic drugs has increased between 1989 and 1997. Many of these cases have been related to pediatrics and have occurred incidentally, so that of the total 22170 patients, 11092 were under 6 and 1799 were between 6 and 19 years old. Also, 17385 patients (78.4%) were incidentally poisoned with these drugs (4). Since patients less than 14 years of age are not admitted to Baharloo

Hospital, this age distribution and the greater incidence of general poisoning is justifiable.

Nevertheless, of the 59 patients in this study, 11(18.6%) were male and 48(81.4%) were female. In Von Moch's study (5), 48.3% of the female and 49.4% of the male patients had sulfonylurea overdose and 53.9% of the female and 41.9% of the male patients had beguanide overdose (the gender of other patients was not identified in this study). Ashkani in his study (6) in Shiraz reported that women have a greater tendency for using drugs for committing suicide than men. In Shekholeslami's study, this tendency seemed to be four times more. Noticing the greater incidence of suicide with drugs for attracting attention in young women, such statistics seem reasonable.

The most common clinical symptoms in our patients were lethargy (57.6%) and drowsiness (32.2%), respectively. Triad hypoglycemia (including hypoglycemia lower than 50 accompanied with symptomatic stimulation or CNS function disturbance which can be treated with glucose administration), as the rarest clinical symptom, was observed in only 6.8% of the patients. These complications were not observed in any of the patients who had used metformin alone. Also, 20% of metformin overdose cases, 11.4% of glybenclamide overdose cases, and 22.2% of overdose cases with metformin and glybenclamide together did not present any clinical symptoms.

Von Moch (5) showed that 40.1% of beguanides overdose cases and 41.4% of sulfonylurea overdose cases did not present any clinical symptoms while minor symptoms were observed in 37.6% of sulfonylurea cases and 32.6% of beguanides overdose cases. Severe toxicity symptoms were seen in 13.4% of poisoning with beguanides cases and 14.4% of sulfonylurea overdose cases. Additionally, high risk toxicity symptoms were found in 4.6% of sulfonylurea overdose cases and in 12.2% of beguanides overdose cases.

In Dalan's study (8), 33.3% of patients that referred with confusion, 40% with degrees of decreased consciousness level, 26.7% with convulsion, and 6.7% with coma. All the



patients had developed some degrees of hypoglycemia due to glybenclamide overdose. In a separate study done on oral hypoglycemic drugs overdose in pediatrics, Spiller (9) found nausea, diarrhea, and vertigo to be present in 3.6, 3.6, and 1.8% of metformin poisoning cases, respectively.

In examination of arterial blood gases, 79.7% of our patients were in normal conditions. Degrees of metabolic acidosis were found in 33.3% of the patients that had used metformin. This complication was also seen in 22.5 of the patients who had used metformin together with glybenclamide and in 5.7% of the patients who had used glybenclamide. Von Moch (5) indicated that lactic acidosis due to metformin toxicity is not very common but it can be accompanied with morbidity and mortality and other severe complications. Spiller (9) demonstrated that arterial blood gases in pediatric metformin poisoning cases were normal and had normal lactate levels, whereas Lalau (10) indicated that severe lactic acidosis and other complications are not related to high serum metformin.

Upon admission, 50.8% of the patients had primary blood glucose levels lower than 70mg/dl. Primary blood glucose levels lower than 40, however, were reported in only 17% of the patients and hypoglycemia was not found in any of the patients who had used metformin alone.

Quadrani (11) indicated that in poisoning with sulfonylurea, hypoglycemia occurs in 27% of the cases. The mean minimum hypoglycemia in these patients was 46.5 mg/dl and the threshold time for hypoglycemia fluctuated between 30 minutes and 16 hours. In our study, however, the minimum blood glucose value during treatment was reported to be less than 70 in 32.2% of the patients of whom 10.2% had blood glucose less than 50mg/dl.

In Dalan's study (8), it was shown that all severe cases of poisoning with glybenclamide were associated with hypoglycemia, whereas Spiller (9) demonstrated that poisoning with metformin alone is not accompanied with hypoglycemia. Noticing the half-life of glybenclamide and its mechanism of effect

which stimulates insulin secretion, severe primary hypoglycemia and its continuation with the initial dose seems to be associated with pancreatic B cells for insulin production.

Of the patients, 93.2% had taken oral hypoglycemic drugs for committing suicide, and the majority of the intentional cases of these drugs abuse occurred in under 30 year old individuals. Incidental usage of these drugs was observed in 6.8% of the patients that aged between 30 and 59 (54.21).

Von Mach (5) showed that 62.7% of sulfonylurea and 60.5% of biguanides overdose cases were intentional and the rest were incidental. Although consumption of oral hypoglycemic drugs in old ages is relatively common, incidental poisoning with these drugs is not quite as common. Reports from AAPCC indicate that the incidence of toxicity with these drugs commonly occurs in pediatrics.

Ashkani (6) also showed that the majority of suicidal cases with drugs occur in the age range of 20 to 29. Although only 69.5% of the patients were hospitalized and got discharged after complete recovery, none of the patients seemed to develop severe toxicity complications such as irreversible neurologic complications or morbidity and mortality. However, since 30.5% of the patients did not accept to be hospitalized and got discharged with their own consent, definitive therapy about their health was not possible. Quadrani's study (11) demonstrated that all patients poisoned with oral hypoglycemic drugs can be cured with supportive medical treatment and neurologic damage does not happen to them.

Von Mach (5), on the other hand, showed that mortality and morbidity occur in 9% of sulfonylurea overdose cases and 6.1% of biguanides overdose cases. It seems that precise diagnosis, early treatment upon poisoning with these drugs, and intravenous administration of glucose or diazoxide in poisoning with sulfonylurea and hemodialysis in poisoning with biguanides can lead to survival and recovery even in severe cases of toxicity.

## CONCLUSION

Poisoning with oral hypoglycemic drugs in our patients usually occurs with glybenclamide and metformin mostly due to the widespread usage and prescription of these drugs by physicians. In this study, a greater number of the patients used glybenclamide.

Glybenclamide overdose results in hypoglycemia that can be severe and long-lasting in the event of using its high doses. Careful monitoring of blood glucose and early treatment with intravenous dextrose can prevent severe consequences of toxicity with this drug which often occur in the brain due to its hypoglycemic effects.

Metformin, on the other hand, does not lead to hypoglycemia but the major complication associated with poisoning with it is lactic acidosis which although not common, it can be hazardous to the patients. Early diagnosis and immediate treatment of these patients, bicarbonate administration, and hemodialysis if needed, can prevent the incidence of severe complications of this type of toxicity.

In addition, using spectometry for urine screening and diagnosis of sulfonylurea toxicity in patients referring with hypoglycemia can be useful and is recommended to be provided at specialized hospitals for toxicity and poisoning.

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