Original Article

Clinical and Laboratory Features of Metformin Intoxication in Suicidal Patients Attending an Intensive Care Unit

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Abstract

Introduction: This study has been performed for the purpose of researching the complications occurred at patients who took metformin overdose in an attempt to suicide. None of the patients has the diagnosis of diabetes mellitus and never used metformin. **Materials and Methods:** This retrospective cross-sectional study was carried out with 21 patients who has neither diagnosed diabetes mellitus nor taken metformin for suicide before. **Results:** It was observed that there is a moderate, negative ($r = -0.63$) statistically significant correlation ($P < 0.001$) between the time of applying to the hospital and arterial blood pH at the arrival and a statistically significant positive mild correlation ($P < 0.041$) between applying and blood lactate level ($r = 0.45$), and a moderate positive ($r = 0.63$) and statistically significant correlation ($P < 0.001$) between the total metformin dose and blood lactate level at the arrival and a positive, moderate ($r = 0.68$) significant correlation ($P < 0.001$) between the creatinine and metformin dose at the arrival. Lactic acidosis has been detected at 8 of 21 patients, 6 patients were hemodialized, 2 patients needed mechanical ventilation, and 2 patients died. It is observed that there is no mortality for early hemodialized patients. **Conclusion:** The most important reason of the mortality in patients who has metformin intoxication is metformin-associated lactic acidosis (MALA). It was considered that hemodialysis therapy could be effective in MALA.

Keywords: *Intoxication, lactic acidosis, metformin-associated lactic acidosis, metformin*

Date of Acceptance:
14-Nov-2017

Introduction

Metformin and phenformin are antiglycemic agents that started being used after 1950s.[1,2]

Metformin is the main biguanide used in clinic. Metformin decreases insulin resistance and hepatic glucose output and increases peripheral uptake.[3] Its clear effect in diabetic patients is that it decreases fasting and postprandial blood glucose at the rate of 20%–40%.[4] It has an effect on body weight decrease but this effect is weak.[5] Half-life of metformin elimination in patients who have good kidney functions is about 5 h. Metformin is removed from the body actively by carriers without being metabolized from the kidney's proximal tubules. It can accumulate in the body in case of kidney failure.[6]

If the serum creatinine level is higher than 1.5 mg/dl, metformin should not be given in the event of distinct tissue hypoxia such as sepsis and myocardial infarction. After contrast agent with iodine is given, metformin should not be given for 3 days and should be restarted after the control of the kidney functions and also it is not recommended to give metformin 2 days before the general anesthesia.[7,8]

The major toxicity of acute and chronic metformin intake is metformin-associated lactic acidosis (MALA).[9]

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_343_16

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How to cite this article: Cetinkaya A, Avci D, Erden A, Akca O, Ozer O, Kalan U, *et al.* Clinical and Laboratory Features of Metformin Intoxication in Suicidal Patients Attending an Intensive Care Unit. Niger J Clin Pract 2018;21:143-8.

Although MALA is a frequent metabolic disorder in critical patients, its real prevalence is unknown.[10,11] Lactic acidosis occurs when the lactate concentration is more than 5 mmol/L and arterial blood pH is <7.35. In critical patients, mortality range is up to 83% due to lactic acidosis.[10,12] In a study, it was determined that lactate level of ≥4 mmol/L caused increase on hospital mortality rate six times with direct proportion of the lactate level.[13] MALA incidence is 2–9/100 000 and mortality rate is higher than 50%/year. In a scientific research accomplished at a tertiary Intensive Care Unit in Australia, MALA incidence was reported as 6 of every 1000 Intensive Care Patient admission. The mortality rate of the patient admission was found as 29%.[14] In another study performed in Europe, MALA incidence rate of all intensive care patient admissions was recorded as 0.84% and the rate of mortality depending on MALA was stated as 30%.[15] A Canadian study investigating the patients using metformin from 1980 to 1995 was recorded the lactic acidosis incidence as 9/100,000.[4] In a research performed by Jan Daniel Lalau in 1999, 49 patients who were diagnosed MALA were investigated and the mortality rate was recorded as 45%.[16] In the meta-analysis done by Shelley R. Salpheter in 2003, lactic acidosis risk at patients taking metformin for Type 2 diabetes mellitus was investigated and lactic acidosis was found 9.9 in 100,000 in the metformin group. According to this study, the risk of lactic acidosis does not increase in type 2 diabetic patients taking metformin when it is compared with the ones who is not taking metformin, but it should not be used in patients carrying risk factors.[5,8]

In the current study, we investigated intoxications of the patients who has no diabetes and who took metformin for the purpose of just suicide not for the treatment.

Materials and Methods

The target population of this retrospective study was the in patients followed by the division of Internal Medicine Intensive Care Unit at Kayseri Training and Research Hospital in Turkey between June 1, 2010 and December 31, 2015 who took metformin for suicide. Our study was conducted due the approval of the Ethical Committee within the number January 19, 2016/49 decision of the training planning council of Kayseri Training and Research Hospital. The files of the 305 patients taking drugs and substance for suicide among the total 4710 inpatients at the Internal Medicine Intensive Care Unit were searched retrospectively. Twenty-one metformin intoxication cases admitted to the hospital with suicide diagnosis were included in the study. Patients using metformin for diabetes or another reason and having chronic diseases (diabetes mellitus, heart failure, chronic kidney failure, and chronic liver disease) were excluded from the study. None of these patients got drugs from drug store so as to attempt suicide. The drugs they took were their relatives'. They did not have difficulty in obtaining metformin and they had this toxic substance in their homes and it was easily accessible.

Demographic (age, sex, and body mass index), clinical (medical history, taken metformin dose, physical examination findings, hospitalization duration at the Intensive Care Unit, Glasgow coma score, duration between the time of taking the drug and arrival at the hospital, treatments, and prognosis) and laboratory data, and the need of ventilator were searched. Laboratory tests included complete blood count, liver function tests, hemostasis tests, blood lactate levels, and blood gas results (pH, HCO_3, pO_2, pCO_2, anion gap, and base excess). The possibility patients received activated charcoal, stomach lavage, positive inotrope agent, bicarbonate treatment, n-acetylcysteine treatments, and hemodialysis therapy was taken into consideration. Whether they needed mechanical ventilator or not was also taken into consideration. The features of the hemodialysis are as follows: 2 more hours are added to the routine dialysis which is 4 h by the polysulfone dialyzer, surface area of hemodialysis filter is 1.6 m^2, dialysis solution includes 138 mmol/L Na, 1.5 mmol/L Ca, 0.5 mmol/L Mg, 110 mmol/LCl, 2 mmol/L acetate, and 33 mmol/L bicarbonate. Blood flow was adjusted as 300 ml/min and dialysate flow was adjusted as 500 ml/min. Hemodialysis machine's trademark was Fresenius Core 408 B (Fresenius Medical Care, Germany).

Statistical analyses

The appropriateness of the variables to the normal distribution was examined using visual (histogram and probability graphics) and analytic methods (Shapiro–Wilk test). We reported continuous data as mean and standard deviation or median and percentiles. The correlation coefficients and statistical significance of the variables were calculated by Pearson's correlation or Spearman's test. If the $P < 0.05$, it should be considered as significant. All statistical analyses were performed using SPSS version 21.0 (Statistical Package for Social Sciences; SPSS Inc., Chicago, Illinois, USA).

Results

Three hundred and five of the 4710 patients admitted to the Internal Medicine Intensive Care Unit between the dates of June 1, 2010 and December 31, 2015 were the ones who took drugs and substance for the purpose of suicide. Twenty-one of these patients took metformin for the purpose of suicide. The demographic

Table 1: Laboratory values of the patients with metformin intoxication

	n	Median	Minimum	Maximum
Age (year)	21	20	16	37
Duration to admission (h)	21	2	0.50	6.00
Total metformin dose (g)	21	20	5	150
BMI (kg/m^2)	21	21.28	17.53	37.8
pH (admission)	21	7.40	7.26	7.48
Lactate (admission) (mg/dl)	21	16	3	48
Lactate (peak) (mg/dl)	21	16	3	68
HCO_3 (admission) (meq/l)	21	20.90	8.00	31.30
Base excess (admission)	21	−3.90	−15.90	−5.10
Anion gap (admission)	21	11.00	6	31
Creatinine (basal) (mg/dl)	21	0.80	0.30	1.20
Creatinine (admission) (mg/dl)	21	0.90	0.30	1.50
Glucose (admission) (mg/dl)	21	95	65	227
WBC (admission) (1×10^3/µl)	21	10,820	1000	14,600

Admission=The measurement in admission; Duration for admission=The duration between the suicide time and the admission time; BMI=Body mass index; pH=Potential of hydrogen; WBC=White blood cells count

Table 2: Distrubition of the patients by the treatment modalities

Treatment received	*n* (%)
Gastric lavage	21 (100)
Activated charcoal	21 (100)
$NaHCO_3$	8 (38.50)
Inotropic agents	3 (14.26)
N-acetylcysteine	1 (4.77)
Hemodialysis	6 (28.57)
Mechanic ventilation	2 (9.54)

Table 3: The correlation table of the study variables

Variables 1	Variables 2	*r*	*P*
Total metformin dose	Lactate (admission)	0.63	0.003
	Lactate (peak)	0.81	<0.001
	HCO_3 (admission)	−0.75	<0.001
	Anion gap (admission)	0.66	0.001
	Creatinine (admission)	0.68	0.001
	WBC (admission)	0.49	0.022
Duration for admission	pH (admission)	−0.63	0.002
	Lactate (admission)	0.45	0.041
BMI	Lactate (admission)	−0.49	0.021
pH (admission)	Duration for admission	−0.58	0.016
Lactate (admission)	Duration for admission	0.48	0.027
Lactate (peak)	Total metformin dose	0.64	0.002
	Base excess (admission)	−0.56	0.018
HCO_3 (admission)	Total metformin dose	−0.75	<0.001
Base excess (admission)	Metformin dose	−0.65	0.001
Anion gap (admission)	Metformin dose	0.67	0.001
	WBC (admission)	−0.54	0.011
Anion gap (peak)	Metformin dose	0.69	0.008
Creatinine (admission)	Total metformin dose	0.68	0.001
	Anion gap (admission)	0.56	0.008
	WBC (admission)	0.50	0.020
WBC (admission)	Metformin dose	0.49	0.022
	pH (admission)	−0.54	0.011
	Lactate (peak)	0.53	0.012
	HCO_3 (admission)	−0.45	0.036
	Base excess (admission)	−0.54	0.011
	Anion gap (admission)	0.61	0.003

Admission=The measurement in admission; Duration for admission=The duration between the suicide time and the admission time; BMI=Body mass index; pH=Potential of hydrogen; WBC=White blood cells count

distribution of these patients was 11 female (54.5%), and 10 male (45.5%), and the median age was 20 (16–37) years.

Medical histories, laboratory values, and the duration of hospitalizing at the Intensive Care Unit were tabulated in Table 1. Treatments administered to the patients were shown in Table 2 and the correlation between the obtained data was shown in Table 3.

Hypoglycemia was seen in 12 patients, neurologic symptoms were seen in 4 patients and hypotension was seen in 10 patients during their application to the hospital and their follow-ups. Gastrointestinal symptoms developed in 21 patients. Nausea and vomiting were seen in 19 patients. There was myalgia in 4 patients. Six patients received hemodialysis therapy. Two patients needed mechanical ventilation. Two patients who had suicide attempt history died.

A statistically significant negative correlation was found between the total metformin dose and initial HCO_3 and a positive correlation between total metformin dose and serum lactate, anion gap, creatinine, and white blood cell count. The other significant correlations were summarized in Table 3. Two patients took another hypoglycemic medicine together with metformin for the purpose of suicide. One of these patients took glibenclamide and the other patient took sitagliptin and acarbose. Hypoglycemia developed at the patient who took glibenclamide. Hypoglycemia did not develop at the patient who took sitagliptin and acarbose. Lactic acidosis was not seen in both of the patients.

Discussion

Intoxications are the major cause of patients applying to the emergency service and Intensive Care Unit and they account for 0.8%–5% of the patients in the emergency service. Many of these intoxications are drug intoxications, and many of these drug intoxications are admitted to the Intensive Care Unit and receive treatment.[17,18] Intoxications are seen most frequently between the ages of 25–35 and the rate of females to the males is 63%/37%.[19] The rate of all drug intoxications

followed in Intensive Care Unit was 6.4%, and the rate of these admissions due to metformin was 6.5%. The median age was 20 (16–37) and the rate of the female to male was 11/10.

Kidney dysfunction is responsible for MALA with nonsuicidal patients.[20,21] In this study, 21 patients took metformin for suicide have not had kidney dysfunction before. The creatinine and leukocyte counts of the patients were specifically high at the first time they applied to the hospital. We found a statistically significant correlation between metformin dose and arrival creatinine level. Leukocyte count was found high when compared with the metformin dose. In some previous publications, it was stated that leukocytosis had been seen in other intoxications.[22] However, we have not detected such a finding for metformin intoxication in literature. There were a positive correlation between metformin dose and lactate in the patients and this was statistically significant. We found a strong and negative statistically significant correlation between the applying period to the hospital and pH. There was a positive moderate correlation between the applying period to the hospital and lactate level, and this was also statistically significant. We have not found out any data to show this relation in the literature. The lactate level and severity of metabolic acidosis increase rate of mortality in MALA.[12,14,15,23] Elevated anion gap with metabolic acidosis can occur in metformin intoxication. Researches indicated that MALA in metabolic acidosis with elevated anion gap is the most important and mortal complication as a result of taking metformin for the suicide purpose.[10,14,15,24] In this study, MALA developed in eight of 21 patients (38%).

We found the rate of general mortality depending on drug intoxications in the Intensive Care Unit was 1%. In this study, the rate of mortality depending on metformin intoxications was 9.5%. We identified the rate of mortality in the patients developed MALA as 25%. The mortality rates from this study should be presented in Table 3. In a study conducted in Europe, MALA incidence in intensive care admissions was found as 0.84% and the rate of mortality depending on MALA was stated as 30%.[15] In this study, mortality rate depending on MALA is similar with Biradar *et al*. study.[15]

In this study, 2 patients died because of MALA. It was determined that the first patient had taken 1388 mg/kg (75 g) metformin and the second had taken 2631 mg/kg (150 g). The average metformin dose that surviving patients had taken was 24.4 g. This confirms that higher metformin dose increases mortality.[20] Whereas the first patient applied to the hospital 5 h after she had taken metformin, the second one applied 6 h later after he had taken metformin. The average applying period of the other patients after they had taken metformin was 1.77 h. The first patient received hemodialysis treatment 7 h after taking metformin but the second could not receive hemodialysis treatment since his general situation was critical and he was in shock despite the high dose of inotrope medicine. Furthermore, both of the patients were administered invasive mechanical ventilation support and sodium bicarbonate treatment. According to our consideration, prolonged applying time to the hospital after taking overdose metformin for suicidal purpose may be one of the mortality reasons for both of these deaths.

The treatment of the metformin intoxication varies according to the physicians. The treatment is adjusted according to the time of admission of the patient to the hospital and the dose of metformin taken. Arıkan *et al*. stated that two patients who took metformin for suicidal purpose and their kidney function were normal but lactic acidosis developed. Both of the patients were treated sodium bicarbonate treatment without hemodialysis.[25] In the series of 5 patients that Avcı *et al*. reported one patient died in spite of hemodialysis. Three of the other patients developed lactic acidosis and they were treated with hemodialysis.[20] In another study it is stated that 3 patients had taken high-dose metformin for suicide followed in mechanical ventilator and administered hemodialysis.[21] In a case presentation, it was reported that a 14-year-old female patient who took 40 g metformin for suicidal intent was cured with early hemodialysis treatment.[26] In another case, a patient who took 48 g metformin and 108 g rosiglitazone for the attempt of suicide was cured successfully with the 39 days mechanical ventilation treatment.[27] Tung *et al*. reported about 2 patients who had taken metformin for suicidal purpose developed metabolic acidosis with elevated anion gap, and one of the patients died. The other patient was cured with early hemodialysis or continuous venovenous hemodialysis (CVVHD) together with other treatments.[28]

Measurement of metformin concentration is not routinely done and it cannot be measured normatively in everywhere. Cantrell *et al*. investigated a patient in postmortem period who had died from metformin intoxication with lactic acidosis. In that study, they found out high-dose metformin concentration in the blood and liver. Besides, even 24 h after the drug intake, a high dose of metformin was found in the stomach. Since metformin intoxication – lactic acidosis is relatively frequent in emergency services; metformin measurement should be routinely done.[16,29]

Under the light of the experiences, we have gained from these patients who developed MALA and the literature review, we immediately started to hemodialysis

treatment in addition to other treatments at the early stage of MALA (this early stage is occurred when pH value is <7.35, HCO_3 is <3.17 meq/l, and blood lactate level is above 5 mmol/dl, [20 mg/dl]) for the patients who took metformin for the intent of suicide. Moreover, according to the patient's arterial blood gas values, metabolic acidosis status was evaluated. At the patients treated with this approach, mortality was not seen and all were discharged with full recovery. In the literature, it is stated that using early hemodialysis or CVVHD decreases mortality rate in the cases of MALA with suicidal patients.[10,21,26,27] As a result, anamnesis should also be questioned insistently for the patients with metabolic acidosis with elevated anion gap considering metformin intake for suicide. Hemodialysis should be initiated for the cases with metformin intoxication as soon as possible to prevent from tissue hypoxia and organ failure and it should be used for a long time as much as possible according to the patient's hemodynamic state. Hemodialysis should not be stopped before the acidosis of the patient is corrected.[20,21] The elimination of half-life of metformin is about 5 h in patients with normal kidney functions.[10] It should be noticed that renal functions can break down later in comparison with basal renal levels in metformin intoxications. Metformin binds plasma protein negligibly.[5,6] Since metformin binds plasma proteins very little, MALA can be cured with hemodialysis or CVVHD quite successfully.[6,16,26] Hemodialysis should be preferred primarily in MALA. According to the case reports, metformin clearance is lower in comparison with conventional hemodialysis.[16,26] However, there are not retrospective studies in hemodynamically unstable patients and in the patients who cannot tolerate hemodialysis.[7,21,22] The case reports support this approach.[7,20-22] In the cases we were following up, we reached the conclusion that early initiated and extended renal replacement therapy for the acidosis may decrease mortality in MALA. We could not compare the treatment form and mortality since we had few cases and our opportunity to study on this matter randomly was very difficult. However, according to the result of our study and our experiences on metformin and other intoxications with 21 cases, it can be considered that early hemodialysis and CVVHD therapies in MALA are the most important and main component of the treatment.

Conclusion

It should be kept in mind, MALA and metformin intake should be questioned in patients applying emergency service with metabolic acidosis with elevated anion gap. MALA is relatively a rare clinical state but with high mortality. It is considered that early initiated hemodialysis therapy might be applied in MALA as an effective treatment form. Measuring the level of blood metformin in the emergency services will provide early diagnosis in patients developing MALA and will help regulate treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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