

Massive Metformin Overdose in Two Subjects with Suicidal Behavior: Brief Communication

İntihar Davranışı Olan İki Olguda Masif Metformin Aşırı Dozu: Kısa Bildiri

Şenay ARIKAN, MD, Assoc.Prof.,^a
Alpaslan TUZCU, MD, Prof.,^a
Mithat BAHÇECİ, MD, Prof.,^a
Mehmet Ali KAPLAN, MD, Assis.Prof.,^a
Deniz GÖKALP, MD, Assoc.Prof.^a

^aDepartment of Endocrinology,
Dicle University Faculty of Medicine,
Diyarbakır

Geliş Tarihi/Received: 13.05.2010
Kabul Tarihi/Accepted: 05.05.2011

Yazışma Adresi/Correspondence:
Şenay ARIKAN, MD, Assoc.Prof.
Dicle University Faculty of Medicine,
Department of Endocrinology,
Diyarbakır,
TÜRKİYE/TURKEY
sarikan@dicle.edu.tr

ABSTRACT Lactic acidosis is a well-recognized side effect of metformin, especially in patients with renal failure. Only a few cases of deliberate self-poisoning with metformin have been described in the literature. The mechanism of metformin-associated lactic acidosis is complex. In the absence of acute overdose, metformin-associated lactic acidosis rarely develops in patients without comorbidities such as renal or hepatic insufficiency or acute infection. We report two patients who had a large dose of metformin in an attempt to harm themselves and presented with lactic acidosis. In our experience, metformin intoxication may lead a high anion gap metabolic acidosis after a suicide attempt. Sodium bicarbonate infusion is able to correct the acid-base metabolism sufficiently in subjects with normal renal functions.

Key Words: Overdose; acidosis, lactic; metformin; bicarbonates

ÖZET Laktik asidoz metforminin özellikle böbrek yetmezlikli hastalarda iyi bilinen bir yan etkisidir. Literatürde planlı olarak kendini metforminle zehirlemeyle ilgili çok az sayıda olgu bildirilmiştir. Metformin ile ilişkili laktik asidozun mekanizması komplekstir. Metformin ile ilişkili laktik asidoz ilacın akut yüksek doz alımı söz konusu değilse, hastalarda renal ya da hepatik yetmezlik ya da enfeksiyon gibi eşlik eden durumlar yoksa nadiren gelişir. Kendilerine zarar vermek için fazla dozda metformin alan ve laktik asidozla gelen iki hastayı sunuyoruz. Bizim tecrübelerimize göre, metformin zehirlenmesi intihar girişiminden sonra yüksek anyon açıklı metabolik asidoza yol açabilir. Böbrek işlevleri normal olan kişilerde sodyum bikarbonat infüzyonu asit-baz metabolizmasını yeterli ölçüde düzeltebilir.

Anahtar Kelimeler: Aşırı doz; asidoz, laktik; metformin; bikarbonatlar

Türkiye Klinikleri J Med Sci 2012;32(2):559-62

Lactic acidosis is the most frightening side effect of metformin. Although the relationship between lactic acidosis and biguanide is well known, lactic acidosis is rarely seen in type 2 diabetic patients taking metformin.¹ The incidence rate of metformin-associated lactic acidosis is 5-9 cases per 100000 patients, but it is still associated with a high rate of mortality.² Metformin and lactate accumulations in patients who use metformin can only be caused by renal and/or hepatic failure or overdose of metformin due to self-poisoning.³ If metformin is ingested in toxic doses or in the case of impaired renal elimination, lactic acidosis does occur even in the absence of tissue hypoxia or any other risk factors. Only a few cases of deliberate self-poisoning with metformin have been described in the literature. We aimed to report two cases of massive metformin overdose ingestion with

suicidal behavior in subjects with previously normal renal functions, which were associated with lactic acidosis and treated with only bicarbonate (NaHCO₃) and fluid replacement.

CASE REPORTS

CASE 1

A 39-year-old man was admitted to the Emergency Department after a deliberate overdose of metformin (70 tablets). He suffered from type 2 diabetes mellitus and he was taking only metformin therapy for one year. He ingested 59.5 g (583 mg /kg body weight) of metformin in a suicide attempt. After three hours, he had complaints of weakness, vomiting, nausea and diarrhea. Initial physical examination and vital signs were normal. In his history, peripheral artery disease and renal dysfunction were absent. Laboratory testing revealed lactic acidosis [pH: 7.27, anion gap: 14 mmol/L, HCO₃:16 mmol/L, lactate 101 mg/dL (11.2 mmol/L)]. Electrolytes were in the normal limits. Serum creatinine was 1.6 mg/dL and BUN level was 34 mg/dL in the first examination (Table 1). Urine analysis was negative for ketones. With these findings, the case was accepted as a metformin-induced lactic acidosis. Metformin was stopped immediately and insulin therapy was initiated for diabetic regulation because of a high plasma glucose level (233 mg/dL). Electrocardiography was normal. Bicarbonate and fluid treatment was given until acidosis recovered. The amount of bicarbonate replacement was calculated with the following formula: Base deficit \times body weight \times 0.3. On the second day of the treatment, laboratory analyses were as follows: lactate: 20 mg/dL, pH: 7.44, HCO₃: 24.5 mmol/L, creatinine: 0.9 mg/dL. On the

seventh day of the treatment, arterial lactate level was 14 mg/dL (1.55 mmol/L), pH: 7.45 and HCO₃ was 23.5 mmol/dL. Reversible acute renal failure with a maximum creatinine of 2.4 mg/dL was observed. Renal functions gradually recovered. There were no chronic diabetic complications or microalbuminuria during the clinical observation. He improved completely and discharged from our hospital on the 20th day of the treatment.

CASE 2

A 19-year-old healthy young girl was admitted because of ingesting large amounts of her father's drug with suicidal ideation. She had ingested 25 tablets of 500 mg metformin (Total: 12.5 g; 250 mg/kg body weight). She arrived to the emergency department six hours after the ingestion of metformin. She had been suffering from vomiting, nausea and abdominal pain for 3-4 hours. On admission, the patient was in a stable condition and her initial plasma glucose level was normal. She was conscious and alert, with a blood pressure 120/80 mmHg, pulse 76 beats per minute, respiratory rate 25 breaths per minute and body temperature 36.3°C. Arterial blood gas analysis showed metabolic acidosis with a high anion gap [pH: 7.22, HCO₃: 17 mmol/dL, anion gap: 13 mmol/L, lactate: 44 mg/dL (4.87 mmol/L)]. Renal functions were monitored. Normal sinus rhythm was detected on electrocardiography. During the clinical course, a reversible acute renal failure with a maximum creatinine level of 1.25 mg/dL was observed 24 hours later (Table 1). Plasma glucose levels were maintained within the normal ranges. Bicarbonate and fluid treatment was continued until her symptoms improved. On the fourth day of the treatment, the arterial lactate level was determined as 14 mg/dL (1.55 mmol/L), pH:7.41 and HCO₃:23 mmol/L. She recovered completely with supportive care. Hemodialysis was not required. She was successfully treated with bicarbonate infusion. The patient was discharged from hospital after six days.

TABLE 1: The laboratory parameters.

	Case 1		Case 2	
	Before treatment	After treatment	Before treatment	After treatment
pH	7.27	7.44	7.22	7.41
Anion gap (mmol/L)	14	N	13	N
HCO ₃ (mmol/L)	16	24.5	17	23
Lactate (mg/dL)	101	14	44	14
Creatinine (mg/dL)	1.6	0.9	1.25	0.7

N: normal range.

DISCUSSION

Self poisoning with massive metformin overdose in patients with psychiatric disorder is rarely reported

in literature.³ Wills et al. reported that the overall prevalence of metformin-associated lactic acidosis was 14 (3.5%) in 398 cases referred to a healthcare facility.⁴ Metformin-associated lactic acidosis occurred in 9.1% of acute mono-overdose and in 0.7% of polypharmacy overdose patients referred to healthcare facilities and it was 16% in the intentional mono-overdoses.⁴ Metformin intoxication leading to lactic acidosis can present with nonspecific symptoms such as anorexia, somnolence, lethargy, nausea, vomiting and epigastric pain. More serious effects are hypotension, hypothermia, respiratory failure and cardiac dysrhythmia. Approximately 60% of the oral dose of metformin is absorbed.⁵ Twenty percent to 30% of the drug is recovered in the feces, but it is primarily eliminated unchanged by the kidneys by means of tubular secretion.⁵ The half-life of metformin is approximately six hours.⁵ Renal failure impairs elimination, increasing the risk of lactic acidosis.⁵ The onset of lactic acidosis is often subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. Hypothermia, hypotension and resistant bradyarrhythmias may also be associated with more marked acidosis.¹ Metformin-associated lactic acidosis is recognized as a serious condition with a poor prognosis that can occur in patients taking chronic metformin therapy with contraindications to the drug, such as renal dysfunction, liver diseases, alcoholism, and cardiopulmonary diseases. Risk factors other than metformin are clearly important in precipitating lactic acidosis.^{1,6} Dehydration in patients taking metformin can lead to metformin-associated lactic acidosis, a potentially fatal condition. It has a reported mortality rate of 30-50%.^{7,8} The main identifiable risk factors for mortality are sepsis, acute cardiovascular events and end-stage hepatic failure. However, we observed that metformin ingestion caused lactic acidosis in two subjects without any precipitating factors before taking massive overdose of this drug. Although renal functions were impaired in both of them and serum creatinine levels increased after overdose of metformin, they completely recovered

after the treatment. The absence of a relationship between the deterioration of renal function, or increase in creatinine concentration and clinical outcome is striking. Remarkably, mild and moderate renal failure may not increase mortality risk. The pathogenesis of metformin-related lactic acidosis is multifactorial and incompletely understood. Metformin can increase lactate production by changing the intracellular redox potential from aerobic to anaerobic metabolism (type B lactic acidosis).² Gluconeogenesis is inhibited by metformin through reduced hepatic uptake of lactate.² The concentration of metformin at which lactic acidosis develops is uncertain. The absence of a relationship between plasma metformin concentration and lactic acid concentration is in accordance with the results of a well-documented case series published by Lalau and Race.⁹ Surprisingly, they found that high metformin concentration had a prognostically favorable effect on survival.⁹ Recently, Yang et al. reported a 43-year-old woman with type 2 diabetes mellitus and chronic renal insufficiency who developed hypoglycemia, hypothermia, tachycardia and lactic acidosis after a suicide attempt with a metformin overdose.¹⁰ They pointed out that early diagnosis and rapid correction of the metabolic acidosis using hemodialysis or hemofiltration, together with concomitant cardiovascular support, and maintenance of blood glucose and core body temperature, provide the possibility of a positive outcome.

Although hemodialysis or hemofiltration are suggested as the first choice for treatment of intoxication due to taking similar amount of metformin, we successfully treated our patients only with intravenous bicarbonate and fluid infusions without any need for hemodialysis or aemofiltration.^{8,11} Hemodialysis should systematically be performed in more severe forms of lactic acidosis which deteriorate despite intravenous bicarbonate therapy.^{12,13}

In the conclusion, metformin intoxication with suicidal intention may lead to metabolic acidosis with a high anion gap. Bicarbonate infusion in suicidal metformin overdose is able to sufficiently cor-

rect the acid-base metabolism in subjects with the normal renal functions. Despite such a high dose metformin, a severe metabolic acidosis that disrupts

the hemodynamic status, e.g. coma, did not develop. Early intervention in the emergency department might have caused this observation.

REFERENCES

1. Lalau JD, Lacroix C, Compagnon P, de Cagny B, Rigaud JP, Bleichner G, et al. Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* 1995;18(6):779-84.
2. Chang CT, Chen YC, Fang JT, Huang CC. Metformin-associated lactic acidosis: case reports and literature review. *J Nephrol* 2002; 15(4):398-402.
3. Chang CT, Chen YC, Fang JT, Huang CC. High anion gap metabolic acidosis in suicide: don't forget metformin intoxication--two patients' experiences. *Ren Fail* 2002;24(5):671-5.
4. Wills BK, Bryant SM, Buckley P, Seo B. Can acute overdose of metformin lead to lactic acidosis? *Am J Emerg Med* 2010;28(8):857-61.
5. Goo AK, Carson DS, Bjelajac A. Metformin: a new treatment option for non-insulin-dependent diabetes mellitus. *J Fam Pract* 1996;42(6):612-8.
6. Shenoy C. Metformin-associated lactic acidosis precipitated by acute renal failure. *Am J Med Sci* 2006;331(1):55-7.
7. Bailey CJ, Turner RC. "Metformin" *N Engl J Med* 1996;334(9):574-9.
8. Fitzgerald E, Mathieu S, Ball A. Metformin associated lactic acidosis. *BMJ*. 2009 Sep 16;339:b3660. doi: 10.1136/bmj.b3660.
9. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* 1999;20(4):377-84.
10. Yang PW, Lin KH, Lo SH, Wang LM, Lin HD. Successful treatment of severe lactic acidosis caused by a suicide attempt with a metformin overdose. *Kaohsiung J Med Sci* 2009; 25(2):93-7.
11. Panzer U, Kluge S, Kreyman G, Wolf G. Combination of intermittent haemodialysis and high-volume continuous haemofiltration for the treatment of severe metformin-induced lactic acidosis. *Nephrol Dial Transplant* 2004;19(8):2157-8.
12. Lalau JD. Lactic acidosis induced by metformin: incidence, management and prevention. *Drug Saf* 2010;33(9):727-40.
13. Guo PY, Storsley LJ, Finkle SN. Severe lactic acidosis treated with prolonged hemodialysis: recovery after massive overdoses of metformin. *Semin Dial* 2006;19(1):80-3.