Case Report / Olgu Sunumu

Metformin associated lactic acidosis resulted in cardiopulmonary arrest: a rare case

Kardiyopulmoner arrest ile sonuçlanan metformin ilişkili laktik asidoz: nadir bir olgu

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ABSTRACT

Metformin is an oral hypoglycemic drug which is commonly used as a first-line agent in the treatment of type 2 diabetes mellitus. In recent studies, metformin drug levels of the patients with mild or moderate renal impairment were found in normal range and also lactate levels were found in normal range. But it's clinical importance increases when the patient had worsening renal function, hepatic insufficiency or acute infection. In these situations, drug levels can increase lactic acidosis leading to life threatening. Here we present a case of metformin associated lactic acidosis resulted in cardiopulmonary arrest.

Keywords: Metformin, lactic acidosis, cardiopulmonary arrest

ÖZ

Metformin, tip 2 diabetes mellitus tedavisinde birinci basamak ajan olarak yaygın olarak kullanılan oral hipoglisemik bir ilaçtır. Son zamanlarda yapılan çalışmalarda, normal aralıkta hafif veya orta derecede böbrek yetmezliği olan hastaların metformin ilaç düzeyleri normal bulundu ve ayrıca laktat düzeyleri normal sınırlarda bulundu. Ancak, hastanın böbrek fonksiyonu, karaciğer yetmezliği veya akut enfeksiyonu kötüleşmesi durumunda klinik önemi artar. Bu durumlarda, ilaç seviyeleri, yaşamı tehdit eden laktik asidozu arttırabilir. Biz burada kardiyopulmoner arrest ile sonuçlanan bir metformin ilişkili laktik asidoz olgusunu sunuyoruz.

Anahtar Kelimeler: Metformin, laktik asidoz, kardiyopulmoner arrest

INTRODUCTION

Metformin is an oral hypoglycemic drug which is commonly used as a first-line agent in the treatment of type 2 diabetes mellitus (1). In recent studies, metformin drug levels of the patients with mild or moderate renal impairment were found in normal range and also lactate levels were found in normal range. But it's clinical importance increases when the patient had worsening renal function, hepatic insufficiency or acute infection. In these situations, drug levels can increase lactic acidosis leading to life threatening (1-3).

In metformin associated lactic acidosis treatment, supportive methods such as mechanical ventilation

and vasopressor treatments are used. Also renal replacement treatments such as hemodialysis and continuous venovenous hemodiafiltration (CVVHDF) are used in order to treat acidemia and increase drug clearance (2,3).

Here we present a case of metformin associated lactic acidosis resulted in cardiopulmonary arrest.

CASE REPORT

A 65-year-old woman with diabetes mellitus, hypertension and coronary heart disease admitted to emergency service with the complaints of nausea, vomiting, diarrhea and anuria. The patient's medications were as valsartan/hydrochlorthiazide160/12,5 mg/day, atorvastatin 40mg/day, metoprolol succinate 50mg/day, acetylsalicylic acid 100 mg/day and metformin 1000 mg/twice a day. The patient was also using insulin detemir 20 units/day and insulin lispro 14 units before every meal and the patient had coronary artery catheterization 5 days ago. In emergency room, the serum glucose level of the patient was 30 mg/dl so that glucagon and 50 ml of 20% dextrose was administered. After the regulation of serum glucose level, the patient was still confused and the blood pressure was 80/45 mmHg. In physical examination of the patient, disorientation and signs of dehydration was observed In biochemical analysis of the patient, serum urea level was 230 mg/dl and serum creatinine level was 7.0 mg/dl. Five days ago, in preoperative testing for coronary angiography the serum creatinine level of the patient was measured as 1.0 mg/dl. The examination of arterial blood gas results was followed on pH: 6.9, HCO3: 6 mEq/L, anion gap: 27 mmol/L, osmolar gap:18mmol/L and lactate: 12.3 mmol/L. Hemodialysis was performed for 2 hours with 3 mcg/kg/min of norepinephrine infusion to maintain blood pressure higher than 90 mmHg systolic. After hemodialysis, the patient became oriented just for an hour. After an hour the patient had confusion and arterial blood gas parameters were changed as pH: 7.0, HCO3;8mEq/L, anion gap 25 mmol/L, osmolar gap: 17 mmol/L and lactate: 11.3 mmol/L. Afterwards, the patient had cardiopulmonary arrest and then resuscitated and intubated. Vasopressin infusion was performed to maintain mean arterial pressure over 60 mmHg. In the differential diagnosis of high anion gap acidosis, first signs were thought to be due to severe sepsis and septic shock. Because of the history of coronary catheterization and revascularization, an acute coronary event leading to cardiogenic shock was considered firstly. However persistence of severe acidosis despite aggressive interventions and normalization of blood pressure, metformin intoxication was most likely the diagnosis. Hypotension, hypovolemia and impaired clearance of the metformin due to angio-tensin-converting enzyme using associated renal dysfunction was strengthened the metformin associated lactic acidosis (MALA) diagnosis.

After cardiopulmonary resuscitation, the patient needed mechanical ventilation due to type IV respiratory failure as a result of shock and acidemia. Because of the persistent acidemia after the first dialysis, hemodialysis was repeated as four hours. With normalization of acid base status hemodynamics improved and vasopressor dose necessity were reduced. The blood culture results of the patient were negative in infectious agents examination. In the setting of cardiac arrest, cardiac biomarkers were analyzed and troponin level was measured highly positive as 5 ng/ml. Slightly elevated ST-T segment changes were observed in the ECG findings of the patient, but the serial ECGs were negative. This elevation was thought to be occurred because of metabolic and post-resuscitative hemodynamic stress due to stable coronary disease. The patient was examined by echocardiogram (ECHO) on day 2. In this, normal cardial wall motions were observed and ejection fraction was calculated as 50%. Norepinephrine and vasopressin were stopped on day 5 and the patient was extubated on day 7. Urinary output increased in day 8 and serum creatinine returned to basal levels on day 20. The patient was discharged from intensive care unit on day 10 and discharged from the hospital on day 25 without any neurological sequel.

DISCUSSION

Today, metformin is a commonly used drug and it is considered to be safe. MALA is a well-known side effect of this drug. results of recent meta-analysis did not find a strong association between MALA and stable chronic renal disease (1-3). This finding is supported by other studies (4-6). However, some case series demonstrated that acute renal and chronic renal failure patients have an increased risk for the complication of using metformin (7,8). Metformin is excreted from the proximal tubules of the nephrons without being metabolized so that, accumulates in renal failure (8).

Metformin associated lactic acidosis should be suspected in the patient who has all of the following five criterias (8).

1. A history of metformin intake,

2. A significantly high lactate level (>15 mmol/L) with a large anion gap (>20 mmol/L),

3. Severe acidemia (pH: 7.1),

4. A very low serum bicarbonate level (<10 mmol/L),

5. A history of renal failure (glomerular filtration rate <45 mL/min or serum creatinine level >2.0 mg/dL).

Diabetics commonly have coronary artery disease and high risk for cardiovascular event. Extreme acidosis decreases ventricular contractility and cardiac output (9). Due to hypotension and severe coronary artery disease, the coronary perfusion of the patient might be impaired down to critical level. Severe decreasing in coronary perfusion and combined with intense acidemia have resulted with pulseless electrical activity and cardiopulmonary arrest. Friesecke et al. (8) showed that, general mortality rates for patients with an arterial blood pH of <7.00 was significantly better (50 vs. 0%) in MALA patients when compared with other causes of lactic acidosis. This result mainly indicates that MALA is treatable by aggressive interventions including dialysis. In a study of Renda et al. (11) demonstrated that the general mortality rate of MALA is 25.4%. Mortality was related to extend of acidosis not renal failure. Most of the patients died, had multiple comorbidities other than renal failure.

In our case, other causes of acute renal failure like dehydration and contrast use co-existed. In these situations acidemia is generally due to uremia and lactic acid levels are not elevated. So the cause of lactic acidemia in our case is probably due to metformin use. However, the application of iodinated contrast medium, which leads to the accumulation of metformin in vivo is one of the principal reasons for MALA (12).

In the present case coexisting coronary artery disease may contribute to lactic acidosis leading to cardiac arrest. Recent studies showed that metformin clearance was found lower in CVVHDF when compared to conventional hemodialysis. So, CVVHDF should only be considered in patients who are hemodynamically unstable and cannot tolerate hemodialysis (13,14). Extracorporeal treatment indicators cover lactate level > 20 mmol/l, pH 7.0, shock, failure of vital support and observing the decrease in consciousness (14). The first signs of MALA are ordinary vomiting and diarrhea (15). MALA may look like sepsis with gastrointestinal symptoms with nausea, vomiting, abdominal pain and leukocytosis. These symptoms may cause the misdiagnosis so there may be many undiagnosed MALA cases in the world. Real incidence of MALA may be controversial. In a review, it was estimated that there were no cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin use (16). In another different study estimating MALA incidence, the incidence was found 19.46 per 100,000 patient-year exposures to metformin. Relative risk of lactic acidosis in patients taking metformin was 13.53 (95% confidence interval 7.88–21.66) compared with the general population (17). In this study all of the cases were associated with acute renal failure.

CONCLUSION

We wanted to represent this case because of rare but important complication of metformin-MALA. Using contrast agent causing acute renal injury can progress to life threatening MALA as in our case. It is important to be aware of this complication in the earliest stage of metabolic acidosis because it is lifesaving. Education of the patients and providers to avoid metformin when there is a risk of renal failure is important to prevent MALA.

DECLARATION OF CONFLICTING INTERESTS

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Consent to participate: Written informed consent was obtained from the patient for publication of the present case report.

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