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Metformin-induced Lactic Acidosis in Type 2 Diabetes Mellitus Patient with Chronic Renal Failure Presenting with Altered Consciousness

Bilinç Bulanıklığıyla Başvuran Tip 2 Diyabet Mellitus ve Kronik Böbrek Yetmezliği Olan Hastada Metformin İlişkili Laktik Asidoz

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Abstract

Metformin is a widely used oral-antidiabetic with positive effects on metabolism. Its effect on carbohydrate metabolism, lipid profile, weight balance and low price makes it the common choice of treatment in developing countries. Although chronic conditions such as chronic renal failure necessitating hemodialysis are contra-indicated for metformin use, current data shows that, when compared to other oral-atidiabetics, metformin is not associated with an increased risk of lactic acidosis. We describe a patient on metformin therapy with hemodialysis treatment for end stage renal disease, presenting to the emergency department with altered mental status. Metformin-induced lactic acidosis was diagnosed and he was treated with hemodialysis.
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Key words: Metformin, diabetes mellitus, lactic acidosis

Özet

Metformin sık kullanılan, metabolizma üzerine pozitif etkileri olan bir oral anti-diyabetik ilaçtır. Karbohidrat metabolizmasına, lipid profiline ve kilo dengesine etkileri ve diğer ilaçlara gore daha ucuz olması gelişmekte olan ülkelerde sıkça kullanılan bir ilaçtır. Hemodiyaliz gerektiren kronik böbrek yetmezliği gibi kronik hastalıklar metformin kullanımı için kontrendikasyon olsa da mevcut bulgular metforminin diğer anti-diyabetik ilaçlarla karşılaştırıldığında laktik asidoz için artmış riskinin bulunmadığını göstermektedir. Bu vakada acil servise bilinç bulanıklığıyla gelen metformin tedavisi ve son dönem böbrek yetmezliği nedeniyle hemodiyaliz uygulanan bir hastayı sunduk. Metformin ilişkili laktik asidoz tanısı konmuş ve hastanın kliniği hemodiyaliz sonrası normale dönmüştür. *(JAEM 2012; 11: 133-4)*
Anahtar kelimeler: Metformin, diyabet, laktik asidoz

Introduction

Metformin is a biguanide group oral anti-diabetic drug used for the treatment of type 2 diabetes mellitus. Compared to other oral anti-diabetics, it is less likely to cause hypoglycemia and its lower cost makes metformin the first line treatment choice in developing countries. Nausea, vomiting, diarrhea, abdominal pain and anorexia are the most common adverse effects encountered during treatment (1). Lactic acidosis is a serious side effect seen with metformin use, and while the incidence of lactic acidosis is similar to other oral-antidiabetics, metformin is not recommended to patients with certain risk factors, such as cardiovascular, pulmonary, and renal and liver failure (2). Here we report a case of metformin-induced lactic acidosis in a type 2 diabetes mellitus patient undergoing hemodialysis due to chronic renal failure.

Case Report

A 51 year old male patient with type 2 diabetes mellitus presented to the University Emergency Department (ED) with altered consciousness. The patient was undergoing hemodialysis three times a week for the last six years due to chronic renal failure. His relatives stated that the patient started having nausea and vomiting a month previously and upper gastrointestinal endoscopy had been performed three weeks earlier with no pathology detected. However, the patient developed slurred speech and drooping eyelids and a neurologist diagnosed Myasthenia Gravis and pyridostigmine (Mestinon 60 mg tablet) therapy was initiated. He was also prescribed metfomin (Glucophage 500 mg tablet) and rosiglitazone (Avandia 4 mg tablet) for diabetes, telmisartan and hydrochlorothiazide (Micardis plus 80 mg tablet) for hypertension and calcium diacetate (Phosex 250 mg tablet) for chronic renal failure.

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Upon admission, his respiratory rate was 22 per minute while his other vital signs were within normal range. He looked moderately ill. Physical examination revealed bilateral rales in lung bases with a Glasgow Coma Scale of E2M5V3 without lateralizing deficit. Biochemistry showed a blood glucose level of 97 mg/dL, blood urea nitrogen 21 mg/dL, creatinine 1.81 mg/dL, sodium 140 mEq/lt, potassium 3.11 mE1/lt, chloride 90 mEq/lt and calcium 9.5 mEq/lt. Computerized tomography to rule out intracranial pathology revealed normal results. Arterial blood gas analyses while the patient was on nasal oxygen showed a pH of 7.39, carbon dioxide partial pressure 14.9 mmHg, oxygen partial pressure 206 mmHg, and bicarbonate 9.3 mEq/lt. Blood gas results were consistent with high anionic gap metabolic acidosis with an anion gap of 40 mEq/lt. The patient's current metformin use was thought to cause lactic acidosis and the lactic acid measurement revealed 11.1 mg/dL lactic acid (normal range 0.7-2.5 mmol/ml).

The patient was diagnosed with metformin-induced lactic acidosis and hemodialysis was initiated. However, hypotension and bradycardia developed during the procedure and positive inotropic support with dopamine and dobutamine was given until the blood pressure was stabilized. After four hours of hemodialysis, lactic acidosis regressed as monitored by blood levels and the patient was internalized to the intensive care unit for further treatment. The patient's level of consciousness improved and Glasgow Coma Scale as assessed after treatment progressed to 14. Lactic acid levels after the hemodialysis and 12 hours after admission to the ED were 0.9 mg/dL and 0.6 mg/dL consecutively. The patient stated that he wanted to continue his renal replacement program as an outpatient and he was discharged after two days in the ICU.

Discussion

Metformin is a biguanide group oral anti-diabetic which has been prescribed since the 1960's. When used alone or in combination with sulphonylureas, it has effects on carbohydrate metabolism as well as weight control, hypoglycemia and serum lipid levels (3).

Lactic acidosis is a rare and potentially fatal condition resulting from tissue hypoperfusion and hypoxia (2). It is characterized by elevated blood lactate levels (>45.0 mg/dL, >5.0 mmol/lt), decreased pH (<7.35) and electrolyte disturbance with an increased anion gap. It is believed that metformin causes lactic acidosis by decreasing the gluconeogenesis of alanine, pyruvate and lactate with the resultant increases in lactic acid. An earlier biguanide compound, pherformin was withdrawn from the market because it caused lactic acidosis with a high incidence of 40-64 cases per 100,000 patient-years (1).

Metformin is contraindicated in cases where there is compromised tissue perfusion such as cardiovascular, pulmonary, renal and liver failure, and this limits its use. Despite clear contraindications, in a study where 308 type 2 diabetes mellitus patients who were on metformin were investigated, 73% of the patients had conditions necessitating discontinuation of metformin therapy (4) and although patients had risk factors for developing lactic acidosis, no patient was reported to have developed lactic acidosis.

In a systematic review of 194 studies which evaluated the risk of fatal and non-fatal lactic acidosis with metformin use in type 2 diabetic patients, the incidence was 8.1 cases per 100.000 patient-years (2). The incidence of lactic acidosis with non-biguanide therapy was 9.9. Eighty studies included in the review did not have renal insufficiency as exclusion criteria and because the true number of patients with impaired renal function included in those eighty studies and excluded in other studies are unknown, authors agree that it is impossible to conclusively analyze the safety of metformin use in patients with impaired renal function. Finally, the authors also maintain that metformin use is not associated with an increase risk of lactic acidosis when compared to other oral-antidiabetics. In a study where type 2 diabetic patients admitted to the ED with nonketotic metabolic acidosis are studied, among those diagnosed with lactic acidosis, 29 patients in every 100 patients were using sulphonylurea, 32 patients were using sulphonylurea and pherformin, 48 patients were on insulin, while the number of patients using metformin was zero (5).

Conclusion

Although it is widely believed that metformin use is associated with lactic acidosis mostly in patients with underlying conditions precipitating metabolic acidosis, the current data does not lend support to this notion. Altered consciousness, often associated with metformin-induced lactic acidosis may be caused by various other conditions including hypoglycemia, cerebrovascular disease, and uremic encephalopathy. However, lactic acidosis must be considered in the differential diagnosis even in the absence of renal insufficiency in patients presenting to the ED with altered mental status while using metformin. The medications patients are on must be meticulously questioned and lactate levels must be determined if metformin is prescribed. If metformin-induced lactic acidosis is diagnosed, hemodialysis is the current treatment of choice.

Conflict of Interest
No conflict of interest was declared by the authors.

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