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Case report

A Rare Outcome Induced by Metformin Intoxication: Severe Lactic Acidosis and Hepatotoxicity

Faruk Elyigit, Harun Akar, Utku Erdem Soyaltın and Ferhat Ekinci

Izmir Tepecik Training and Research Hospital, Department of Internal Medicine, Izmir, Turkey

Abstract

Metformin is a widely used oral anti-diabetic agent that decreases insulin resistance. Lactic acidosis rarely develops with this medication. Metformin-induced hepatotoxicity has been rarely reported in the literature. We describe a patient, who presented with lactic acidosis and hepatotoxicity after ingestion of 40 pills of metformin in order to commit suicide. The most important treatment step in patients with metformin-associated lactic acidosis (MALA) is high-volume hemodialysis and hemofiltration.

Keyword: metformin intoxication, dialysis, hemofiltration, lactic acidosis

Introduction

Metformin is a biguanide anti-diabetic drug that is widely used in the treatment of type 2 diabetes mellitus. Lactic acidosis is a rare but serious adverse effect of metformin especially in patients with renal failure. Advanced age, liver disease, alcoholism or cardiopulmonary disease can cause lactic acidosis or metformin accumulation. Metformin is absorbed quickly by the intestines and is not metabolized. About 90% of the drug is eliminated by glomerular filtration and tubular secretion [1,2]. The mechanism by which metformin causes acidosis and hepatotoxicity is not entirely understood. In this report we describe a 19-year-old female patient who presented with lactic acidosis, elevated liver enzymes and alterations in the coagulation tests after metformin overdose.

Case Report

A 19-year-old female patient presented to the emergency department with complaints of nausea and vomiting after ingestion of 40 pills of metformin (850 miligram), 4 pills atorvastatin and 4 pills dexsketoprofen in order to commit suicide. Nasogastric tube was inserted and gastric lavage was performed with activated charcoal. She was

Table. 1. Laboratory values of the patient

Initial tests		7th day		14th day	
Glucose	73 mg/dl	Glucose		Glucose	87 mg/dl
Urea	25 mg/dl	Urea	24 mg/dl	Urea	20 mg/dl
Creatinine	1.1 mg/dl	Creatinine	0.8 mg/dl	Creatinine	0.8 mg/dl
Sodium	139 mEq/L	Sodium	141 mEq/L	Sodium	140 mEq/L
Potassium	4.0 mEq/L	Potassium	4.3 mEq/L	Potassium	4.3 mEq/L
Aspartate aminotransferase (AST)	19 IU/L	Aspartate aminotransferase (AST)	82 IU/L	Aspartate aminotransferase (AST)	17 IU/L
Alanine aminotransferase (ALT)	12 IU/L	Alanine aminotransferase (ALT)	91 IU/L	Alanine aminotransferase (ALT)	24 IU/L
Total bilirubin	1.23 mg/dl	Total bilirubin		Total bilirubin	0.9 mg/dl
Direct bilirubin	0.21 mg/dl	Ddirect bilirubin		Ddirect bilirubin	0.15 mg/dl
Amylase	131 IU/L	Amylase		Amylase	70 IU/L
White blood cell	16800 /UL	White blood cell	7300 /UL	White blood cell	
aPTT	19.9 sc	aPTT	21 sc	aPTT	21 sc
PT	18 sc	PT	13 sc	PT	15 sc
INR	1.6	INR	1.1	INR	1.3 sc
pH	7.33 mmHg	pH	7.44 mmHg	pH	
pCO2	32 mmHg	pCO2	36 mmHg	pCO2	
HCO3	9.6 mmol/L	HCO3	25 mmHg	HCO3	
Lactate	4.7 mmol/L	Lactate	0.9 mmHg	Lactate	

Correspondence to: Faruk Elyigit, Izmir Tepecik Training and Research Hospital, Department of Internal Medicine, Izmir, Turkey; E-mail: frk6535@gmail.com

conscious and alert, with blood pressure 100/60 mm Hg, pulse rate 80 beats per minute and body temperature 36°C. There was no significant finding in the physical examination. Initial blood tests revealed glucose 73 mg/dl, urea 25 mg/dl, creatinine 1.1 mg/dl, sodium 139 mEq/L, potassium 4.0 mEq/L, chloride 110 mEq/L, aspartate aminotransferase 19 IU/L, alanine aminotransferase 12 IU/L, total bilirubin 1.23 mg/dl, direct bilirubin 0.21 mg/dl, amylase 131 IU/L, white blood cell 16.800/UL. Arterial blood gas showed acidosis (pH: 7.3 mmHg, pCO2: 32 mmHg, pO2: 70 mmHg, HCO3: 9.6 mmol/L, SatO2: 78, lactate: 4.7 mmol/L, anion gap: 23.4 mmol/L). Initial serum coagulation profile revealed an INR of 1.6 and a PT of 18 seconds. Her acidosis was tried to be controlled with NaHCO3. She was admitted to the hemodialysis (HD) unit where she was treated with 2 hours of HD. Then she was transferred to the intensive care unit due to her depressed alertness. She was treated with hemodiafiltration (HDF) for 24 hours. The patient's level of consciousness returned to normal, lactic acidosis was improved and then she was transferred to the general medical ward.

On the fifth hospital day, elevation of liver enzymes were noticed-AST: 91 IU/L and ALT: 82 IU/L (Table 1). The patient was found clinically to have metformin intoxication with mild hepatoxicity and prolongation in INR and PT on the initial presentation. Markers of autoimmune and viral hepatitis were all negative. The patient underwent abdominal ultrasound that revealed normal findings. N-acetylsysteine and ursodooxycholic acid were started. The symptoms and abnormal laboratory tests of the patient gradually normalized with supportive treatment. Seven days after her admission, the patient was discharged with mild elevations in liver enzymes levels.

Discussion

Metformin is a biguanide commonly used in type 2 diabetics and is considered to be a safe drug with minimal side effects. The anti-hyperglycemic effect of metformin is caused by a decrease in hepatic glucose production, a reduction in intestinal glucose absorption, an increase in insulin sensitivity and an elevation in peripheral glucose uptake and utilization [1].

Lactic acidosis is one of deadly side effects of metformin intoxication [3]. Pathogenesis of metformin-associated lactic acidosis (MALA) is considered to increase intestinal lactate production after accumulation of metformin in the gastrointestinal system associated with using these drugs [3]. In intensive care patients mortality rates have been demonstrated to be as high as 80% [4].

There is no effective antidote in the treatment of MALA. For this purpose parenteral NaHCO3, continuous venovenous hemodiafiltration (CVVHF) and intermittent hemodialysis are frequently applied methods [5]. Hemodialysis corrects acidosis and also removes metformin from plasma reducing lactate production rate [2].We applied these methods in our patient and received positive results; lactic acidosis improved. Although metformin-associated gastrointestinal discomfort and lactic acidosis is a widely recognized side effect of this drug, metformin-induced liver injury has been rarely reported [1,6,7]. Although pathophysiology of hepatotoxicity is unclear, Zheng suggested that metformin-induced liver injury was associated with concomitant intake of other hepatotoxic drugs, in most of the reported cases as in our case. Although rare, metformin can be responsible for inducing liver damage [7]. Nammour reported a case with metformin-induced cholestatic hepatitis, treated with discontinuation of the drug, and liver enzymes normalized except for a persistently increased level of alkaline phosphatase, most likely related to a prolonged cholestatic effect of metformin [7]. Hashmi suggested that in published cases with metformin-induced hepatotoxicity the number of reported cases on this subject was underestimated, probably due to the lack of a consistent terminology [8]. Because metformin is not metabolized in the liver, it has been considered safe from a hepatic standpoint; however, metformin hepatotoxicity has rarely been reported [9,10]. Possible mechanisms of injury are direct, idiosyncratic, or a drug-drug interaction leading to acute hepatocellular and/or cholestatic jaundice [9,11].

Akinci *et al.* showed a temporary decrease in proteins of the coagulation system synthesized by the liver with no effect on the coagulation factors produced by the endothelium [12]. Probably, prolongation in our patient's coagulation parameters might reflect a temporary defect in hepatic function.

The most important treatment step in patients with MALA is high-volume hemodialysis and hemodiafiltration [5]. A few case reports related with hepatotoxicity have been associated with metformin usage.

Packer *et al.* reported a case with fulminant and fatal hemolysis that occurred shortly after metformin was started for treatment of type 2 diabetes mellitus [13]. Boyd *et al.* suggested that diabetic heart failure patients with elevated systolic blood pressure are at an increased risk of developing acute decompensated heart failure, which is often associated with decreased kidney function [14]. It is well known that patients with concurrent conditions, including advanced age, liver disease, alcoholism, cardiopulmonary disease or renal failure, which in themselves can cause lactic acidosis or metformin accumulation [15]. Since renal function can appear to be normal when measured by serum-creatinine concentration in older patients with reduced muscle mass, calculation of GFR often reveals impairment, and metformin is contraindicated in these patients with poor renal function [16]. MALA should also be considered in the acutely unwell diabetic patients on metformin [17].

The initial presentation of this patient would suggest a picture of MALA. Classically metformin overdose has

been found to produce lactic acidosis. This case illustrated that we should also be aware of the potential rare side effects of metformin as hepatotoxicity, cholestatic hepatitis and hemolytic anemia. Routine workup of metformin overdose should include liver enzymes and tests for coagulation and hemolysis.

Conflict of interest statement. None declared.

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