Case Report

Lactic Acidosis due to Metformin Overdose. What treatment should be? A Case Report and Review of the Literature.

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Abstract

Background. Metformin is one of several oral biguanides that are used for the treatment of diabetes mellitus Lactic acidosis in metformin use is awidely recognised with rare side effect. Patients with previously normal renal function and younger patients with no other comorbid conditions at all might develop metformin induced lactic acidosis.
Case presentation. A 25-year-old healthy woman ingested 100 g of metformin in a suicide attempt. After 3 hours; she, was admitted to hospital with nause, vomiting, abdominal discomfort complaints. At admission, she was anxious and agitated, with following finding; Total Glasgow Coma Scale score of 15 out of 15, pulse rate of 84 beats/min, blood pressure of 80/50 mmHg, and respiratory rate of 20breaths/min. Analysis of arterial blood gases revealed a high anion gap, 16.2 mEq/L metabolic acidosis with pH 7.16, pCO_2. 35.4 mm Hg, pO_2 of 119.5 mmHg on oxygen (2L/min), Lactate 6.55 mEq/L and Bicarbonate: 15.7 mEq/L.
Regarding the drug history, clinical and laboratory findings, the patients was admited to intensive care unit (ICU) with the suspicion of metformin-associated lactic acidosis .
The patient was treated on an emergency basis and received fluid management, intravenous sodium bicarbonate and activated charcoal, 100 g orally in first four hours after admission, The patient follow-up, reversibl acut renal failure was developed (maximum creatinine: 1.66 mg/dl). The bicarbonate ampoules were added to 5% dextrose, so, the patient's glucose level was not low Initially, the decrease in bicarbonate level and pH, lactate levels increased. After the treatment, acid-base balance improved. Two days later, she was transfered to a general medical ward, ICU follow-up was not necessary. She was discharged in good clinical condition 5 days Address for correspondence:
Conclusion. High anion gap metabolic acidosis and increased serum lactate level in patients should be a reason for metformin associated lactic acidosis suspicion.
We present a case of successful management of metformin-associated lactic acidosis, treated simply, with intravenous sodium bicarbonate and intensive monitoring.
This relatively noninvasive method is an effective treatment option.

Keywords: metformin, lactic asidosis, bicarbonate treatment

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Introduction

Metformin is an oral hypoglycemic drug that in the presence of insulin suppresses hepatic gluconeogenesis and improves insulin's action. Its association with lactic acidosis is rare with an estimated incidence of 6.3 per 100.000 patient years. Intentional metformin overdose is also rare, especially metformin associated lactic acidosis in diabetic patients who have renal or hepatic insufficiency. Most cases have been described in therpeutic use, and very few of them have been described in over dose. It is reported that overdose with metformin might result in lactic acidosis in healty patients, a condition that is associated with a high mortality of 50-80% [1,11].

Case report

A 25-year-old healthy woman ingested 100 g (1.94 g/kg body weight) of metformin in a suicide attempt. After 3 hours; she, was admitted to hospital with nause, vomiting, abdominal discomfort complaints. The patients had no comorbid conditions (diabetes mellitus, renal dysfunction, congestive heart failure etc).
At admission, she was anxious and agitated, with following finding; Total Glasgow Coma Scale score of 15 out of 15, pulse rate of 84 beats/min, blood pressure of 80/50 mmHg, and respiratory rate of 20 breaths/min. Other clinical examinations unremarkable. Preliminary laboratory studies WBC: 14.560 mm^3 Hb: 12.5g/dl, PLT: 270.000 mm^3, Na 142,mEq/L, K 4,35 meq/L, CI:115 mEq/L, urea: 17 mg/dL, creatinine: 0.83 mg/dL, glucose: 110 mg/dL. Analysis of arterial blood gases (ABG) revealed a high anion gap, 16.2 mEq/L (8 -16 mEq/L) metabolic acidosis with pH 7.16 (7.35-7.45) pCO_2. 35.4 mmHg (35-45 mmHg), pO_2 of 119.5 mmHg on oxygen (2L/min) (80-100 mmHg), Lactate 6.55mEq/L (0.44-2.22) and Bicarbonate: 15.7 mEq/L (21-28 mEq/L). Liver function

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tests and amylase were within normal ranges, and ketones we was not detected in either serum or urine.

Regarding the drug history, clinical and laboratory findings, the patients was admited to intensive care unit (ICU) with the suspicion of metformin-associated lactic acidosis (MALA).

The physician at the Poison Control Center was recommended standart gastrointestinal decontamination, serial ABG with aggressive correction of the metabolic acidosis with bicarbonat drip and consideration of early hemodialysis.

The patient was treated on an emergency basis and received fluid management, intravenous sodium bicarbonate (1 mEq/kg) and activated charcoal, 100 g orally in first four hours after admission, Early hemodialysis was not applied because of her renal function was not markedly impaired and a life-threatening metabolic acidosis, was not identified.

The patient follow-up, reversibl acut renal failure was developed (maximum creatinine: 1.66 mg/dl). The bicarbonate ampoules were added to 5% dextrose, so, the patient's glucose level was not low Initially, the decrease in bicarbonate level and pH, lactate levels increased. After the treatment, acid-base balance improved. Two days later, she was transfered to a general medical ward, ICU follow-up was not necessary. She was discharged in good clinical condition 5 days later (Table 1).

Table 1. Arterial blood gases and creatinine results of patient

	Emergency	ICU enteran	2 hours later	6 hours later	12.hours later	ICU Second day	Before externed
pH	7.16	7.24	7.22	7.27	7.30	7.44	7.44
HCO_3 (mEq/L)	15.7	11.7	9.7	13.1	14.4	24.5	28.4
Lactat(mEq/L)	6.55	17.7	hıgh	hıgh	15	7.7	3,4
AnGap (mEq/L)	16.2	27,3	35,5	36.8	31.7	22.8	18.4
Creatinine(mg/dl)	0,83	0,64			1,66	1,13	0,72

1. Intensive care unit or in service hospitalizations of patients as a routine consent form is signed; 2. The patient does not want to write name, including shortening; 3. Permission for publication was taken from the patient

Discussion

Metformin is one of several oral biguanides that are used for the treatment of diabetes mellitus. Biguanides act to lower serum glucose levels by inducing decreasing gastrointestinal absorption carbohydrates, inhibiting hepatic gluconeogenesis, and increasing cellular up take of glucose. Metformin is absorbed relatively quickly at the intestinal level, is not metabolized, and 90 % of the drug is eliminated by glomerulofiltration and tubular secretion. Protein binding of metformin is negligible. The mean volume of distribution is 63 to 276 litres. These two properties of metformin mean that haemodialysis or haemofiltration can effectively remove metformin from serum. Its half life is around 6.5 hours in patients with a normal renal function [2].

MALA is rare with an estimated incidence of 6.3 per 100,000 patients years, mostly in patients with predisposing factors. Significant renal and hepatic disease, alcoholism and conditions associated with hypoxia (eg. Cardiac and pulmonary disease, surgery) are contraindications to the use of metformin. Other risk factors for metformin-induced lactic acidosis are sepsis, dehydration, high dosages and increasing age [1].

The physiopathology of MALA is complex and mostly unclear. However, this side effect seems to be closely related to the anti-hyperglycaemic effect of metformin. It is also known that metformin impairs lactate clearance of the liver through the inhibition of complex I of the mitochondrial respiratory chain.

Although increased lactic acid production may be induced by haemodynamic instability and/or tissue hypoxia associated with severe metformin overdose or any underlying unstable cardiovascular or respiratory condition, lactic acidosis is predominantely due to a lack of lactate's clearance than to an increased production [3].

Lactic acidosis was defined according to the criteria of Luft: arterial lactate>5 mmol/l and blood pH<7,35. Clinically, disorders of lactate metabolism have been divided into either anaerobic (type A) or aerobic (type B). The hallmark of type A lactic acidosis is tissue hypoxia resulting in anaerobic lactic acid production. The most common causes of type A lactic acidosis are cardiopulmonary arrest and other states characterized by impaired cardiac performance, reduced tissue perfusion, and arterial hypoxemia. In type B lactic acidosis, on the other hand, it appears that tissue hypoxia is not present, and, instead, lactic acid production is enhanced metabolically for other reasons in an otherwise aerobic state. Examples of type B lactic acidosis include diabetes mellitus, certain malignancies, and congenital diseases of the liver that impair lactic acid metabolism. Of the two forms of lactic acidosis, type A is by far the more important clinical problem [4].

Signs and symptoms of biguanide-induced lactic acidosis are nonspecific and include anorexia, nausea, vomiting, altered level of consciousness, hyperpnoea, abdominal pain and thirst. Hypotension, hypotermia, hypoglycemia and respiratory failure have been described [5].

Salpeter et al. reviewedall studies of metformin treatment 1966 up to 2005.Their data revealed no cases of fatal or nonfatal lactic acidosis. Also,there was no difference in lactate levels between metformin and placebo or other treatment groups.They concluded that there is no evidence that metformin is associated with an increased risk of increased lactate levels or lactic acidosis. Nevertheless, over the last years, several case reports have been published on association between metformin and lactic acidosis [1].

Here we present the case a woman, who attempted to commit suicide by ingesting an 100g massive metformin overdose associated with lactic acidosis, in the absence of other causes of lactic acidosis. The patients had been suffering from gastrointestinal symptoms prior to admission. These symtoms could have been side effects of metformin or first signs of a developing lactic acidosis.

The management of MALA is controversial. Treatment may include supportive care, activated charcoal, bicarbonate infusion, hemodialysis, or continuous venovenous hemofiltration. Activated charcoal can absorb metformin and prevent absorption by the intestines so it is recommended in treating metformin overdose. The administration of agents such as methylene blue and sodium dichloroacetate has gained attention, but their clinical significance and efficacy are controversial and have yet to be evaluated [2].

Bicarbonate therapy for severe lactic acidosis remains a controversial therapy. The most recent Surviving Sepsis Guidelines of 2008 strongly recommend against the use of bicarbonate in patients with pH at least 7.15, while deferring judgment in more severe acidemia. Cooper *et al*. Monitored fourteen patients who had metabolic acidosis (bicarbonate <17 mmol/L and base excess <-10) and increased arterial lactate (mean, 7.8 mmol/L), Each patient sequentially received sodium bicarbonate (2 mmol/kg body weight). Correction of acidemia using sodium bicarbonate did not improve hemodynamics in critically ill patients who had metabolic acidosis and increased blood lactate [6].

Hemodialysis has been shown to facilitate clearance of lactate and ketones from the circulation in patients with biguanide-induced metabolic acidosis. However, the effectiveness of haemodialysis in the treatment of biguanideinduced lactic acidosis is a function of the quantity of biguanide that has been ingested. Multiple haemodialysis treatments may successfully remove the majority of metformin and buformin from the tissues [7]. Haemodialysis is appealing as it can buffer acidosis and theoretically extract metformin from blood. Unfortunately, this technique has not gained widespread acceptance due to the lack of well-conducted studies. Indeed, only case reports have dealt with this subject [8,9].

Peters and et. systematically evaluated outcomes in MALA patients admitted to their intensive care unit. The mortality rate of patients who received dialysis was similar to that of patients who were not dialyzed. However, it was the more acutely and chronically ill patients who actually received dialysis [10].

Conclusıon

Metformin induced lactic acidosis may occur in patients with previously normal renal function, a condition that is a associated with a high mortality of 50-80% [11]. High anion gap metabolic acidosis and increased serum lactate level in patients should be a reason for metformin associated lactic acidosis suspicion.

In cases of metformin induced severe refractory lactic acidosis, Early haemodialysis or hemodiafiltration should be considered to –correct acidosis and eliminate metformin.This approach is very effective and can be life saving [8,12]. But here we present a case of successful management of metformin-associated lactic acidosis, treated simply, with intravenous sodium bicarbonate and intensive monitoring. This relatively noninvasive method is an effective treatment option. However, hemodialysis still has a valuable role in the management of acidosis which proves refractory to conservative treatment.

Conflict of interest statement. None declared.

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