Case Report

Metformin Induced Lactic Acidosis in a Patient with Anorexia Nervosa: A Case Report and Literature Review

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ABSTRACT

Severe lactic acidosis is a rare but life threatening complication of metformin, particularly in patients with renal failure. The mortality rate of metformin induced lactic acidosis is about 50%. Metformin is usually prescribed in type 2 diabetes and is a recognized cause of lactic acidosis in predisposed diabetic patients. We present a case of anorexia nervosa (AN) admitted with severe lactic acidosis and acute renal failure induced by six months of self medication with metformin attempting further weight reduction. The patient was volume resuscitated and started on bicarbonate infusion. She underwent immediate hemodialysis with rapid and prompt recovery. The relation between metformin induced lactic acidosis and anorexia nervosa is not known before. Reversible tubular dysfunction that may mimic Fanconi syndrome has been documented in one report. AN can be considered an additional risk factor for metformin induced lactic acidosis.

KEY WORDS: anorexia nervosa, lactic acidosis, metformin

INTRODUCTION

Lactic acidosis is a serious clinical condition associated with high mortality. Lactic acidosis is particularly found in conditions associated with impaired tissue oxygenation (type A, e.g., shock states) and those in which a systemic impairment in oxygenation is not apparent (type B). Metformin, commonly used in patients with type 2 diabetes, is rarely associated with lactic acidosis (type B) with an average incidence of 0.03 per 1000 patient-years and mostly in patients with associated renal, hepatic, cardiac or respiratory failure, dehydration and elderly diabetics[1]. If the underlying cause of lactic acidosis can be reversed, lactate will be metabolized and acidosis will resolve. This explains the high mortality rate in such patients. Very rarely however, lactic acidosis can occur as a result of metformin therapy in the absence of pre-existing risk factors as reported in this case.

CASE REPORT

A 20-year-old female patient was admitted to Farwania Hospital with one day history of generalized fatigue, nausea, vomiting, abdominal pain and severe shortness of breath. She was admitted three months earlier with severe weight loss and amenorrhea, and diagnosed as a case of anorexia nervosa (AN). However, she rejected follow up with the psychiatrist. At that time she gave history of taking metformin for weight reduction and she had normal renal and liver function in addition to normal blood glucose measurements. She has a strong family history of diabetes mellitus. Her father, mother and sister were diabetics on metformin.

On admission, she was confused, hyperventilating and emaciated. Her blood pressure was 90/60 mmHg, pulse 127/min, temperature 35 °C with poor peripheral circulation (cold, cyanosed extremities and mild pedal edema). Her weight was 27 kg and height 162 cm with a body mass index (BMI) of 10.3 kg/m² (normal BMI: 18.5-24.9).

Her initial laboratory findings were as follows: ABG: pH= 6.8 (normal:7.35-7.44), PO2 = 172 mmHg (normal:70-100), PCO2= 9 mmHg (normal:35-45), HCO3 = 4 mmol/l (normal:21-28). The results of her laboratory investigations are shown in Table 1.

The patient was started on intravenous fluid, sodium bicarbonate and noradrenaline infusion, in addition to massive replacement of calcium, magnesium, phosphorus, folate, vitamins B1, B6, B12 and other trace elements.

The diagnosis of metformin induced lactic acidosis was made and hemodialysis was initiated immediately. She was evaluated by the surgical service and they excluded a surgical abdomen.
clinically and by abdominal ultrasound. Next
day, patient was fully conscious with improving
hemodynamics and rising serum pH and
bicarbonate. She developed a picture of DIC
(prolonged PT, PTT, PLT count dropped to 44x10^9,
low fibrinogen, high FDP) and transient diffuse
ECG changes. On the second day, her urine output
improved, serum creatinine dropped to 177 mg/l
and the DIC parameters normalized. She was further
managed in the medical ward and gradual oral
feeding was started with supplementary calcium,
vitamin D, folic acid and multivitamins without
any complications. The patient was under medical,
psychiatrist and dietitian’s care in the medical ward
for two months and discharged with improving
nutritional parameters.

DISCUSSION
Metformin (dimethylbiguanide) is an orally
administered drug used to lower blood glucose
concentrations in patients with type 2 diabetes.
Metformin therapy causes a small increase in basal
and postprandial blood lactate concentrations,
within the normal range. The interpretation of these
increases, however, needs to take into account the
fact that obesity and diabetes slightly raise blood
lactate concentrations. The increased blood lactate
concentrations are probably caused by metformin-
induced conversion of glucose to lactate by the
intestinal mucosa. The lactate then enters the portal
circulation and is largely cleared by the liver, in
which it serves as a gluconeogenic substrate[1]. When
the liver is inundated with fuels after a meal, more
lactate gains entry into the systemic circulation[2,3].

Lactic acidosis is a rare but serious adverse effect
in metformin-treated patients, with an estimated
incidence of less than 0.01 to 0.08 cases (average,
0.03) per 1000 patient-years. In most patients it
occurs because one or more contraindications were
overlooked, predominantly renal insufficiency,
leading to high plasma metformin concentrations.
Additional factors that increase blood lactate
concentrations are often present — for example,
a major illness causing hypotension with low
tissue perfusion, other causes of hypoxia, liver
disease, or alcohol abuse. In these situations the
plasma metformin concentration is not necessarily
abnormally high. It is important to realize that
blood lactate concentrations become elevated in
any patient in whom cardiogenic shock or other
illnesses decrease tissue perfusion, and in some
reported cases, the metformin was probably an
incidental factor and not responsible for the lactic
acidosis. Nevertheless, under conditions impairing
the oxidative removal of lactate, the reduced rate
of removal of lactate from plasma resulting from
decreased conversion of lactate to glucose by
metformin could cause excessive increases in plasma
lactate and, possibly, lactic acidosis[1]. The etiology
of lactic acidosis in the reported case is probably
multifactorial including hypotension, volume
depletion, hypothermia, (all due to anorexia nervosa
with the subsequent impairment in renal and hepatic
function) and probably metformin overdose. The
mortality in reported cases is about 50 percent. The
risk of death from lactic acidosis in metformin-
treated patients is similar to that of hypoglycemia
in sulfonylurea-treated patients. Should a patient
have lactic acidosis attributable to metformin, the
drug can be removed by hemodialysis[1].

There have been reports of decreased platelet
sensitivity to aggregating agents during metformin
therapy, possibly due to reduced blood glucose
concentrations. Increased fibrinolytic activity and
small reductions in plasma concentrations of the
fibrinolytic inhibitor plasminogen-activator
inhibitor type 1 have also been described[4,5]. The
DIC picture developed in the reported case could
be explained by the severe lactic acidosis and
hypothermia.

Table 1: Laboratory investigation results

<table>
<thead>
<tr>
<th>Laboratory Investigation</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (Random)</td>
<td>1.3</td>
<td>6.7 - 11.1 (mmol/l)</td>
</tr>
<tr>
<td>Sodium</td>
<td>126</td>
<td>140 - 148 (mmol/l)</td>
</tr>
<tr>
<td>Potassium</td>
<td>6.5</td>
<td>3.6 - 5.2 (mmol/l)</td>
</tr>
<tr>
<td>Chloride</td>
<td>96</td>
<td>100 - 108 (mmol/l)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>3</td>
<td>21 - 32 (mmol/l)</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.75</td>
<td>2.2 - 2.62 (mmol/l)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.67</td>
<td>0.81 - 1.58 (mmol/l)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.69</td>
<td>0.74 - 0.99 (mmol/l)</td>
</tr>
<tr>
<td>Albumin</td>
<td>32</td>
<td>34 - 50 (g/l)</td>
</tr>
<tr>
<td>Amylase</td>
<td>100</td>
<td>25 - 115 (u/l)</td>
</tr>
<tr>
<td>Hb</td>
<td>101</td>
<td>117 - 154 (g/l)</td>
</tr>
<tr>
<td>MCV</td>
<td>102</td>
<td>77 - 91 (fL)</td>
</tr>
<tr>
<td>WBC</td>
<td>15.4</td>
<td>4 - 11 * (10^9/L)</td>
</tr>
<tr>
<td>PLT</td>
<td>317</td>
<td>150 - 440 * (10^9/L)</td>
</tr>
<tr>
<td>ESR</td>
<td>10</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>PT</td>
<td>17</td>
<td>12 - 14 (seconds)</td>
</tr>
<tr>
<td>APTT</td>
<td>37</td>
<td>30 - 40 (seconds)</td>
</tr>
<tr>
<td>FDP</td>
<td>&gt; 1000</td>
<td>&lt; 500 (ng/ml)</td>
</tr>
<tr>
<td>Lactate</td>
<td>26.7</td>
<td>0.5 - 2.2 (mmol/l)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>331</td>
<td>53 - 115 (umol/l)</td>
</tr>
<tr>
<td>Urea</td>
<td>22</td>
<td>2.5 - 6.4 (mmol/l)</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>161</td>
<td>50 - 136 (u/l)</td>
</tr>
<tr>
<td>ALT</td>
<td>972</td>
<td>30 - 65 (u/l)</td>
</tr>
<tr>
<td>Random Cortisol</td>
<td>1750</td>
<td>160 - 1000 (nmol/l)</td>
</tr>
<tr>
<td>B12</td>
<td>1200</td>
<td>174 - 878 (pg/ml)</td>
</tr>
<tr>
<td>Serum Folate</td>
<td>13.5</td>
<td>3 - 17 (ng/ml)</td>
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<tr>
<td>RBC Folate</td>
<td>614</td>
<td>93 - 641 (ng/ml)</td>
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<tr>
<td>25 OHVITD</td>
<td>12</td>
<td>23 - 113 (nmol/l)</td>
</tr>
<tr>
<td>iPTH</td>
<td>8.9</td>
<td>1.1 - 7.3 (pmol/l)</td>
</tr>
<tr>
<td>TSH</td>
<td>0.9</td>
<td>0.27 - 4.2 (uIU/ml)</td>
</tr>
</tbody>
</table>

DIC picture developed in the reported case could
be explained by the severe lactic acidosis and
hypothermia.
AN is an eating disorder that usually begins in adolescence. Among patients who have AN in adolescence, medical complications may persist into the adult years. No particular nutritional regimen has proved to be superior, as long as adequate calories are supplied. Brisk improvement in nutritional status with few complications resulting from re-feeding occurs when inpatients are started with 1200 to 1500 kcal per day and the intake is increased by 500 kcal every four days to about 3500 kcal (for female patients) and to 4000 kcal (for male patients) per day.

Supplemental overnight naso-gastric feeding may slightly decrease the length of the hospital stay among children but is not routinely recommended. Close monitoring is needed during starvation and re-feeding, including monitoring of vital signs and attention to serious complications that require urgent intervention (e.g., prolonged QT interval or hypophosphatemia with associated weakness, confusion, and progressive neuromuscular dysfunction). This syndrome is most common among patients weighing less than 70 percent of their ideal body weight and in those receiving parenteral or enteral nutrition, although it can also occur in those receiving vigorous oral re-feeding. Slower re-feeding minimizes the risk of serious complications. Phosphorus, magnesium, and electrolyte levels and renal function should be closely followed, and supplements should be administered as needed. Short-term medical stabilization alone is inevitably insufficient. To achieve full remission, ongoing care after discharge from the hospital is essential.

AN has been associated with abnormal osmoregulation and impaired urinary concentrating capacity. Conflicting results suggest that the disorder may be related to hypothalamic dysfunction and/or a primary renal defect. The role of antidepressants, which are increasingly prescribed in AN patients, has not been evaluated. AN has been associated with various renal function abnormalities, including a decline in glomerular filtration rate (GFR), an impaired water diuresis, a decreased urinary concentrating capacity and various electrolyte abnormalities. Reversible tubular dysfunction that mimics Fanconi syndrome has also been described in one report.

In conclusion, lactic acidosis is a serious complication of metformin use in diabetic patients if not used selectively. The relationship between metformin and anorexia nervosa in patients not known to be diabetic has not been described before, but, it makes sense to avoid it in such patients given the fact that AN can cause complications virtually affecting every organ system.

REFERENCES