Severe Metformin Intoxication With Lactic Acidosis In An Adolescent: A Case Report

M Gura, S Devrim, A Sagroglu, Z Orhon, B Sen

Abstract

A 14-year-old girl has taken 45 gr (0.75 g kg\(^{-1}\) body weight) of metformin in a suicide attempt. The first arterial blood gas showed a marked metabolic acidosis with a high lactate level and subsequently she developed moderate renal failure. The lactic acidosis was successfully treated with early continuous venovenous hemodiafiltration. After 16 h of haemofiltration, the arterial pH steadily increased back to normal levels, and lactic acidosis improved. It is concluded that patients with severe lactic acidosis secondary to metformin overdose should be treated promptly with hemofiltration.

INTRODUCTION

Metformin is a biguanide class drug. Biguanides have been used for many years as oral anti-hyperglycemic agents in the treatment of type II diabetes mellitus. These agents exert their action by increasing cellular insulin sensitivity. Lactic acidosis is a rare but serious adverse effect of metformin, especially in patients with renal failure. Severe lactic acidosis is a recognised and often fatal complication of metformin overdose. Metformin is absorbed relatively rapidly by the intestine and is not metabolised. About 90% of the drug is eliminated by glomerular filtration and tubular secretion with a serum half-life between 1.5 and 5 hours. There are several case reports of metformin overdose in the literature but intoxications with metformine in childhood are rare. In this report we describe a 14 year old healthy girl who developed lactic acidosis after ingestion of a metformin overdose.

CASE REPORT

The 14-year-old girl took 45 gr (0.75 gr kg\(^{-1}\) body weight) of metformin in a suicide attempt. When she was admitted to the emergency department, she had a Glasgow Coma Scale Score of 13-15. Her body temperature was 36.2 0C. Arteriel pressure was 110/60 mmHg, heart rate 77 beats min\(^{-1}\), respiratory rate 15 bpm. Initial blood tests revealed blood glucose 140 mg dl\(^{-1}\), blood urea nitrogen 17 m gdl\(^{-1}\), creatinine 1.4 mg dl\(^{-1}\), sodium 145 mmol L, potassium 5.4 mmol-1L. The first arterial blood gas interpreted a marked metabolic acidosis with a high lactate level (Table 1). Liver and renal function tests except creatinine and potassium (creatinine:1.4, potassium:5.4) were within normal limits. The patient was thus transferred to the intensive care unit. Four hours later, creatinine and lactat level increased, blood glucose and pH levels decreased (Table1). Initial treatment included 100 ml 20% dextrose iv and 151.2 mEq L sodium bicarbonate iv (8.4% sodium bicarbonate) in 4 hours. Subsequently continuous venovenous hemodiafiltration (CVVHF) with 1.36 % dextrose dialysat, via a double-lumen femoral dialysis line was commenced. Continuous venovenous hemofiltration was performed with a blood flow of 100 mlmin\(^{-1}\) and dialysate flow of 1.5 Lh\(^{-1}\). She developed high blood glucose levels for about 20 hours. So regular insulin was administered 2 IU h\(^{-1}\) (Table 1). Fortytwo hours after CVVHF was commenced, pH, serum bicarbonate, blood glucose, and serum lactate levels returned to the normal limits. Then the CVVHF was stoped. Four days after admission to the ICU, the patient was dismissed from ICU.
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DISCUSSION

Lactic acidosis is a broad-anion gap metabolic acidosis caused by lactic acid overproduction or utilization. It is called “metabolic acidosis” if blood pH is less than 7.35, serum lactate is more than 2 mmol L⁻¹, with disturbances of electrolytes with an increased anion gap. The Cohen-Woods classification categorises causes of lactic acidosis as follows:

- Type A: Decreased perfusion or oxygenation
- Type B: B1: Underlying diseases (sometimes causing type A)
- B2: Medication or intoxication
- B3: Inborn error of metabolism

Lactic acidosis caused by oxygen deficits is generally termed type A (fast-an aerobic) lactic acidosis (type A LA). Lactate metabolism disorder without hypoxia is termed type B (slow-aerobic-type B LA). The character of type A LA is associated with tissue hypoxia, as occurs in sepsis, and type B is associated with systemic disorders such as liver diseases, malignancies, drugs and toxins that impair the metabolism of lactate.

Putative risk factors for lactic acidosis with biguanide treatment as are follows: age of >60 year, decreased cardiac, hepatic or renal function, diabetic ketoacidosis, surgery and respiratory failure, ethanol intoxication, and fasting.

The mechanism of metformin-associated lactic acidosis is not understood yet. Though it is known that it accumulates in the intestine, leading to an increased production of lactate, which lowers the pH within the liver and decreases lactate metabolism by suppressing pyruvate carboxylase. It also decreases glucose utilization and increases lactate production by hepatocytes. Lactic acidosis can be caused by metformin even in patients treated with therapeutic doses. The overall mortality rate of metformin associated lactic acidosis is estimated about 30-50%. This occurs most commonly in patients with significant underlying medical problems especially renal insufficiency and is associated with more than 50% mortality. Mortality does not correlate well with either lactate levels or metformin levels.

The signs and symptoms of metformin overdose associated with lactic acidosis (MALA) are nonspecific and include anorexia, severe nausea, vomiting, diarrhea, epigastric pain, thirst, somnolence, lethargy and hyperpnea. Hypotension, hypoglycemia, pancreatitis, hypothermia, lactic acidosis, acute renal failure, coma and cardiac arrest are significant clinical features. Our patient had nausea, vomitus and lactic acidosis. Case reports of metformin overdose are rare and most of them have been associated with a fatal outcome (therapeutic range lead 0.5-2.5 mcg ml⁻¹). The first report of lactic acidosis associated with metformin exposure in childhood was presented by Lacher and coll. The patient they presented was a 15 year old girl who ingested 38.25 g (0.55 gr kg⁻¹ body weight) of metformin in a suicide attempt. She developed lactic acidosis and moderate renal failure. She was treated with haemodialysis. There are only a few reports of metformin intoxications and their effects in pediatric patients. It is probably due to the fact that the drug is not licenced for use in children. One multicentre case series of paediatric metformin ingestion is based on case reports to American poison control centers. In this study 37 children were evaluated in a healthcare facility. The absolute doses ingested in this study ranged from 250 mg to 16.5 g with a mean of 1.71 g. None of these children experienced hypoglycemia or acidosis. In our patient both hypoglycemia and acidosis were observed.

The treatments of MALA is important in intensive care patients because of the mortality rates as high as 80%. Although there is no consensus about the treatment of the MALA, volume expansion, i.v. sodium bicarbonate, intermittent haemodialysis and high volume CVVHF with a bicarbonate substitute are recommended. Sodium bicarbonate alone frequently fails to correct the acidosis. Survival appears to be better in patients treated with early high volume CVVHF or haemodialysis. Haemodialysis acts a great in role in and removal of the metformin from the circulation, thus preventing further acidosis. The patients...
may be haemodynamically unstable to tolerate
haemodialysis. In that case, haemofiltration seems to be the
better option. Our patient was treated with CVVHF with
blood flow rates of 100 ml min−1 and ultrafiltration flow
rates of 1.5 L h−1 (25 ml kg. h−1). It successfully restored
serum pH and lowered the serum lactate level in 8 hours.
Simultaneously 151.2 mEq sodium bicarbonate (NaHCO3)
was administered intravenously.

Barrueto and coll.8 reported a patient who was 58 year old
type II diabetic man ingested 40.5gr-1 metformin tablets. He
presented severe lactic acidosis. CVVHD was performed for
him with a blood flow of 180 ml min−1 and dialysate flow
of 2.5 L h−1.

Chu and coll 9 described a 75 year old diabetic woman with
acute renal failure and life-threatening lactic acidosis due to
metformin intoxication. Clinical manifestations included
vomiting, diarrhea, hypotermia, hypotension and transient
blindness. She was treated with hemodialysis, also.

Heaney and coll.10 presented a healthy young man who took
a large dose of metformin together with a smaller dose of
nabumetone and glibenclamide in a deliberate attempt to
harm himself. The overdose was associated with a profound
lactic acidosis. He was successfully treated with
haemodialysis carried out with bicarbonate buffer.

Perrone and coll. 11 described 3 patients with metformin
toxicity. Two of three patients were prescribed metformin
despite end-stage renal disease. All patients had lethargy,
vomitting, abdominal pain and elevated serum lactate levels.
Despite sodium bicarbonate therapy and hemodialysis
metformin associated lactic acidosis was fatal in two of the
patients.

Guo and coll. 12 reported two cases of severe lactic acidosis
due to massive metformin ingestion. One of them ingested
45 g and the other ingested 50 g metformin. Both of them
had severe lactic acidosis (blood pH 6.8, lactate 25.7 mEqL,
HCO3-1 4 mEqL and blood pH 6.85, lactate 28.4 mEq L,
HCO3-1 3 mEqL respectively). Despite intravenous
bicarbonate therapy the patients decompensated and were
placed on hemodialysis. They accomplished a complete
recovery.

Al-khasawneh and coll. 13 reported a 44 year old non-obese
male with type II diabetes mellitus. He had attempted to
commit suicide by ingestion of metformin (dose unknown).
He was drowsy but responded to painful stimuli.
Laboratuary findings were; potassium:6.1, bicarbonate:10
mEq L−1, blood urea nitrogen:15 mg dl-1, creatinine :2.3
mg.dl-1, glucose:9 mg.dl-1, anion gap: 26 and lactate: 20
mmol L−1. He was treated with 5% dextrose in water with
150 mEq of NaHCO3-1. Intermittent slow flow dialysis was
performed for more than 3 days to control the lactic acid
level and metabolic acidosis. The patient received iv
dopamine to keep his mean arterial pressure >60 mmHg.
Serum lactate levels peaked at 31 mmol L. 12 hours after
admission. He was transferred from ICU after three days.

Dell’aglio and coll. 14 reported a patient who represented
the largest reported amount of ingested metformin, the
lowest serum pH and the highest serum lactate concentration
in any intestinal metformin overdose survivor in the
literature. The patient was a 40 year old woman who claimed
to ingeste 75 -100 grams of metformin and subsequently
developed severe lactic acidosis. She eventually developed a
peak serum lactate level of 40 mmol L and a serum pH of
6.59 and was hypotensive and hypothermic. After aggressive
supportive therapy with mechanical ventilation, vasopressor
agents, sodium bicarbonate and hemodialysis, her metabolic
derangements steadily improved and she made a complete
recovery without any residual sequelae.

De Pont and coll 15 reported a 39 year old woman with type
II diabetes mellitus, presented with metabolic acidosis due to
an attempted suicide with metformin. Despite treatment with
activated charcoal and laxation, she experienced cardiac
arrest and required SPELLING. After transfer to another
hospital, she was treated with high volume continuous
venovenous hemofiltration. However, she died due to
multiple organ failure.

Considering these reports, our patient had a high risk of
fatality. Possibly, the lack of additional risk factors and the
rapid initiation of haemofiltration were important for her
survival.

As sodium bicarbonate infusions alone are not able to
correct the acid-base metabolism sufficiently, haemodialysis
is recommended for clearance of metformin and treatment of
acidosis. The use of sodium bicarbonate is well known but
controversial. There are theoretical disadvantages of using
intravenous bicarbonate including a left shift of the
oxyhaemoglobin dissociation curve, excess sodium load,
rebound metabolic alkalosis, disturbances in serum
potassium and calcium levels and reflex vasodilation after
bolus injection. The advantage of dialysate with bicarbonate
is the possibility of metformin clearance without any
associated risk of intravenous administration. In our case,
she was treated successfully CVVHF with %1.36 dextrose dialysate.

As a consequence, metformin overdose should be directed with regular monitoring of renal function. Patients with severe lactic acidosis should be treated with hemofiltration or haemodialysis. But hemofiltration would have been able to remove lactate more efficiently.

References