

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

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Citation

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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 lactat 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 insülin 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.

Figure 1

Table 1: Laboratory and arterial blood gas findings

| | Admission | 4 h | 8 h | 12 h | 16 h | 24 h | 48 h |
|-------------------------------------|-----------|-------|-------|------|------|------|------|
| pH | 7,24 | 7,16 | 7,28 | 7,4 | 7,43 | 7,44 | 7,41 |
| Base excess (mmol ⁻¹ .l) | -18.3 | -19.9 | -14.3 | -2.9 | -3.1 | -0.8 | 1.2 |
| Serum lactate | 10,7 | 11,5 | 9,4 | 4,1 | 3,2 | 2,1 | 0,6 |
| Serum bicarbonate | 12 | 10 | 13,5 | 22 | 21,8 | 23,7 | 23,4 |
| Glucose | 140 | 47 | 167 | 172 | 163 | 131 | 82 |
| Creatinine | 1.4 | 2.3 | 1.9 | 1.4 | 0.9 | 1.1 | 0.96 |
| Potassium | 5.4 | 6.1 | 5.6 | 4.8 | 3.31 | 3.4 | 3.2 |
| Sodium | 145 | 145 | 141 | 132 | 139 | 141 | 138 |

DISCUSSION

Lactic acidosis is abroad-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. 1 The Cohen-Woods classification categorises causes of lactic acidosis as follows: 2

- 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- anaerobic) 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, malignencies, 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 functions, 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 .3 It is excreted largely unchanged by the kidneys. 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. 3.

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. 3 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) .4 The first report of lactic acidosis associated with metformin exposure in childhood was presented by Lacher and coll. 5 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.6 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% .7 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.⁸ 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, hypothermia, 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, vomiting, 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. Laboratory 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 ingest 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 resuscitation. 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

1. Chu C-K, Chang Y-T, Lee B-J, Hu S-Y, Hu W-H, Yang D-Y. Metformin-associated lactic acidosis and acute renal failure in a type 2 diabetic patient. *Arch Intern Med.* 1992;152:2333-36.
2. Luft C F. Lactic acidosis update for critical care clinicians. *Journal of American Society of Nephrology.* 2001; 12 (suppl 1): s15-s19
3. Galea M, Jelacin N, Bramham K, White I. Severe lactic acidosis and rhabdomyolysis following metformin and ramipril overdose. *British J of Anaesthesia.* 2007; 98(2):213-15
4. Nisse P, Mathieu-Nolf M, Deveaux M, Forceville X, Combes A. A fatal case of metformin poisoning. *J Toxicol Clin Toxicol.* 2003; 41:1035-36.
5. Lacher M, Hermanns-Clausen M, Haeffner K, Aeffner K, Brandis M, Pohl M. Severe metformin intoxication with lactic acidosis in an adolescent. *Eur J Pediatr.* 2005;164:362-365.
6. Spiller HA, Weber JA, Winter ML, Klein-Schwarz W, Hofman M, Gorman SE et al. Multi-center case series of pediatric metformin ingestion.. *Ann Pharmacother.* 2000; 34:1385-88
7. Spiller HA, Weber JA, Winter ML, Klein-Schwarz W, Hofman M, Gorman SE et al. Bicarbonate haemodialysis as a treatment of metformin overdose. *Nephrol Dial Transplant.* 1997; 12:1046-47
8. Barrueto F, Meggs WJ, Barchman MJ. Clearance of metformin by hemofiltration in overdose. *J Toxicol Clin Toxicol.* 2002; 40:177-180
9. Barrueto F, Meggs WJ, Barchman MJ, Chu C-K, Chang Y-T, Lee B-J et al. Metformin-associated lactic acidosis and acute renal failure in a type 2 diabetic patient. *J Chin Med Assoc.* 2003; 66:505-508
10. Heaney D, Majid A, Junor B. Bicarbonate haemodialysis as a treatment of metformin overdose. *Nephrol Dial Transplant.* 1997; 12:1046-47
11. Heaney D, Majid A, Junor B, Perrone J, Phillips C, Galeski D. Occult metformin toxicity in three patients with profound lactic acidosis. Doi:10.1016/j.jemermed.2007.11.055
12. Heaney D, Majid A, Junor B, Perrone J, Phillips C, Galeski D et al. Severe lactic acidosis treated with prolonged hemodialysis: recovery after massive overdose of metformin. *Seminars in Dialysis.* 2006; 19(1):80-3.
13. Al-khasawneh K, P White. Lactic acidosis secondary to metformin over-dose. *Chest.* 2006; 130(suppl 4), s 337
14. Dell'aglio DM, Perino LJ, Todino JD, Algren DA, Morgan BW. Metformin overdose with a resultant serum pH of 6.59: Survival without sequelae. Doi:10.1016/j.jemermed.2007.09.934
15. de Pont AC, Kerver ED, Jansen ME, Bijleveld YA, Franssen EJ, Hoekstra JB. Fatal auto-intoxication with metformin. *Ned Tijdschr Geneesk* 2007; 151:981-84

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