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HIGH ANION GAP METABOLIC ACIDOSIS IN SEVERE DELIBERATE POISONING WITH METFORMIN – SUCCESSFUL TREATMENT WITH 2.5-HOUR CONVENTIONAL HEMODYALISIS

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Metformin-associated lactic acidosis is a rare, life-threatening condition with a high mortality rate, that could occur both with therapeutic use and in metformin overdose. Clinical manifestations may be nonspecific, with severe anion gap metabolic acidosis and elevated lactate levels being the most prominent laboratory findings; hence, delaying the diagnosis and treatment. Renal replacement therapy plays a key role in the treatment of severe metformin poisoning. We herewith present a case with intentional metformin poisoning successfully treated with one session of hemodialysis in combination with parenteral sodium bicarbonate therapy.

A 17-year-old non-diabetic woman ingested 25 grams of metformin in a suicide attempt. She developed vomiting and diarrhoea and was brought to the local emergency unit, and shortly after admittance she became nonresponsive. Glasgow coma scale was 7/15 (E_2, V_1, M_4), glucose level was 3.4 mmol/L and blood pressure was 90/60 mmHg. The first arterial blood gas analysis demonstrated a severe metabolic acidosis with high lactate level (pH = 6.778, BE -31.7, lactate 18 mmol/L, anion gap 39.8 mmol/L), and, subsequently, she developed a non-oliguric renal failure. Lactic acidosis was successfully treated with a combination of a conventional 2.5-hour bicarbonate HD and early administration of intravenous bicarbonate. The arterial pH steadily increased back to normal levels, lactic acidosis improved and kidney function recovered completely.

It could be concluded that even a single session of timely applied conventional HD in combination with parenteral administration of bicarbonates allows simultaneous drug removal, lactate reduction and acid-base correction and should be a treatment of choice in hemodynamically stable patients with severe metformin poisoning.

Key words: metformin poisoning, lactic acidosis, renal replacement therapy

Introduction

Metformin is widely used and is the most frequently prescribed oral antidiabetic drug of the biguanide family [1]. Its use is generally safe and well tolerated.

Metformin-associated lactic acidosis (MALA) occurs infrequently with therapeutic use of the drug, occurring in 0.03 cases per 1000 patients-years [2]. It is a type of high anion gap metabolic acidosis, and is most often associated with an intercurrent disease and renal insufficiency [3]. MALA is associated with numerous complications and a mortality rate of about 30% in the most severe cases [4]. In overdose cases, however, metformin is frequently associated with lactic acidosis [5, 6]. Reported mortality rate in patients with intentional metformin overdose and severe acidosis (pH less than 6.9) is higher and approaches 83% [7]. Management of metformin overdose includes conservative measures, bicarbonate therapy, and several types of renal replacement therapy (RRT). We describe a case of severe lactic acidosis following intentional metformin self-poisoning, successfully treated with aggressive medical pH correction and early performed conventional 2.5-hour bicarbonate hemodyalisis (HD).

Case presentation

A 17-year-old woman with no history of diabetes ingested 25 grams of metformin in a suicide attempt, according to hetero-anamnestic data. The patient had a history of depression, including prior suicide attempt by benzodiazepine ingestion. She discontinued prescribed medications (sertraline) several months earlier. Two hours after deliberate ingestion of 25 g metformin (50 metformin tablets of 500 mg), medication used by her grandmother, patient developed vomiting and diarrhoea and was brought to the local emergency unit. Shortly after admittance she became nonresponsive. Initial vital signs, as recorded by emergency team, were temperature 36.2^0C, heart rate 74 beats/min, BP 90/60 mmHg, respirations 25 per minute, oxygen saturation 99% via puls oxymetry on room air. Glasgow coma scale (GCS) was 7 (Eye opening response to pain - 2, Verbal response-no response - 1, Motor response - flexion withdrawal from pain - 4). Pupils were equal and reactive, and oral mucous membranes were dry. Initial laboratory findings were unremarkable. Electrocardiogram did not show any abnormalities. Tracheal intubation was performed for airway protection. She was administered activated charcoal lavage through nasogastric tube and 20 ml 8.4% sodium bicarbonate intravenously. After 4 hours glucose level decreased to 3.4 mmol / L, heart rate increased to 110 beats/min, and became profoundly hypotensive. After being treated with intravenous bolus of 35 % dextrose and 10% dextrose intravenous infusion, she was transferred to the University Clinic of Toxicology. On admission, her BP was 65/45 mmHg and normal saline infusion with 20 ml of 8.4% sodium bicarbonate and dopamine was administered. Her BP increased to 100/50 mmHg and heart rate was 130/min. She was somnolent but oriented, and GCS was 13 (E-3, V-5, M-5). Initial investigations revealed non-oliguric acute renal failure with blood urea nitrogen 8.4 mmol/L, creatinine 158 μmol/L, sodium 130.2 mmol/L, potassium 6 mmol/L, ionized calcium 1.09 mmol/L, chloride 98 mmol/L, glucose 27.7 mmol/L, and blood lactate 18 mmol/L. Complete blood count revealed leucocytosis with a left shift (WBC from 17.500 to 60.800/mm^3, PMN 80%) First arterial blood gas analysis demonstrated a severely wide anion gap acidosis with high lactate level (pH = 6.778, pCO2 = 3.07 kPa, pO_2 = 14.32 kPa, HCO_3 3.3 mmol/L, base deficit (BE) -31.7 mmol/L, anion gap 39.8 mmol/L, lactate 18 mmol/L).

A 2.5-hour session of bicarbonate hemodyalisis was performed few hours after admission. Two ampoules of Ca-gluconate, a total of 220 ml (11 ampoules of 20 ml) 8.4% sodium bicarbonate in intravenous infusion, and parenteral antibiotics were also prescribed, after which the patient's condition gradually improved and stabilized. Arterial blood pH increased to 7.41, BE increased to 1.4 mmol/L. and blood lactate level decreased to 2.2 mmol/L four days after admission (Table 1). Additional investigations, such as abdominal ultrasound, chest X-ray, blood, stool and urine culture were unremarkable. Because no focal infection was detected, antibiotics were stopped on the seventh hospital day. Renal function improved and woman was discharged in a stable condition on the tenth hospital day with a recommendation for extended treatment in the department for adolescent psychiatry.

Table 1. Arterial blood gas results and lactate levels after HD and bicarbonate infusion

	1 day Before HD	1 day After HD	3 day	4 day
pH	6.778	7.234	7.48	7.41
pCO2 (kPa)	3.07	3.39	4.25	4.87
pO2 (kPa)	14.32	10.34	10.75	11.49
HCO3 (mmol/L)	3.3	10.9	24.3	23.4
BE (mmol/L)	-31.7	-14.2	2.0	-1.4
Lactate (mmol/L)	18.00	NA	5.46	2.2

NA-Not available

Discussion

Metformin is the current biguanide of choice for the treatment of type 2 diabetes, particularly in overweight patients. It is also used in the treatment of prediabetes and polycystic ovary syndrome. The antihyperglycemic effect is due mainly to inhibition of hepatic gluconeogenesis and glycogenolysis, and increased insulin-mediated glucose disposal [8], which is followed by a low risk for hypoglycaemia [9].

After ingestion, metformin is completely absorbed from gastrointestinal tract within 6 hours. Bioavailability after oral administration is 50-60% [10]. The volume of distribution is lower at the beginning of treatment, so that by chronic application it is increased tenfold. This is probably due to the distribution of metformin outside the plasma and penetration into other tissues such as the kidneys, liver, pancreas, including erythrocytes. This two-compartment distribution model leads to variations in the elimination half-life of the drug. Metformin is not metabolized in the body. Because plasma protein binding is negligible, the drug is dialyzable. Also, about 90% of the absorbed drug is efficiently eliminated unchanged in the urine.

At therapeutic doses, metformin is a safe drug and is well tolerated. The most common adverse effects associated with its use are disorders of the gastrointestinal tract, such as nausea, vomiting, abdominal discomfort, decreased appetite and metallic taste in the mouth. However, the occurrence of lactic acidosis is a known complication of metformin treatment, but is less frequent. It occurs if patients have contraindications that are overlooked, and in particular the existence of renal failure leading to the accumulation of metformin in plasma. The presence of other severe diseases that lead to hypotension or hypoxia may be the cause of increased lactate concentrations without compulsorily high concentrations of metformin [11].

In cases of metformin poisonings, metformin concentrations rapidly increase, and consecutive lactic acidosis is more frequent and more profound. Development of MALA have nonspecific clinical manifestation such as: diffuse abdominal pain, vomiting, watery diarrhea, decreased level of consciousness. Circulatory instability requiring vasopressors and inotropic agents, leucocytosis without definite focus of infection, hypothermia, cardiac arrhythmias, and respiratory failure treated with mechanical ventilation have also been reported [11, 12]. Some of these effects are consequences of severe academia.

A commonly asked question is whether the increased lactate or metformin levels have a prognostic significance for the occurrence of mortality. In the case of metformin-treated patients with lactic acidosis, according to reports of Lalau et al. [13, 14], neither the first nor the second parameter have a great prognostic meaning, since a patients who survived in both studies had higher metformin concentrations. He concluded that in patients with MALA and similar lactate levels, there is association

with higher concentrations of metformin with less serious comorbidities and a better prognosis. According to him, the prognosis depends more on the severity of the existing comorbidities.
In the cases of intentional metformin overdose, serum lactate level was considered as a good predictor in drug overdose mortality [15]. In other cases, mortality was associated with profound hypotension resistant to therapy and multi-organ failure associated with academia [11]. According to Seidowsky A, the best predictive factor for mortality were an acute liver dysfunction as assessed by prothrombin time [3].
In the absence of available antidote, the treatment of MALA consists of: symptomatic and supportive measures, prevention of additional absorption of the drug in the gastrointestinal tract by applying active charcoal, treatment of competitive diseases if present, correction of metabolic acidosis and acceleration of lactate metabolism, as well as elimination of metformin.

Correction of metabolic acidosis plays a key role in therapy. The use of bicarbonate therapy in patients with metabolic acidosis is still controversial for several reasons. First, data from the literature confirm that in cases where metabolic acidosis is accompanied by comorbidities leading to tissue hypoxia, venous pH decreases during bicarbonate administration [16]. Recent literature reports also suggest that bicarbonate treatment contributes to the paradoxical reduction of intracellular pH [17]. Due to the possibility of lactates and ketone bodies being converted into bicarbonates as the clinical situation improves, the authors suggest an individualized therapeutic approach in patients with acute lactic acidosis and ketoacidosis, and bicarbonates should be given at arterial pH less than or equal to 7 [17]. However, bicarbonates are still widely used in the treatment of metformin poisonings to correct metabolic acidosis, which can be deduced from the available literature. We used high doses of bicarbonate as an intravenous infusion, that resulted in gradual normalization of acidosis and improvement of clinical signs.

Renal replacement therapy is a preferred method for treatment of severe metformin intoxication, as it provides simultaneous removal of the drug from the blood, as well as correction of metabolic acidosis and lactate concentration.

The most recent recommendations for extracorporeal treatment of metformin poisoning suggest starting RRT in the most severe cases, where standard supportive measures have failed. Recommended criteria for initiation of RRT are: lactate concentration > 20 mmol/L, pH ≤ 7, presence of shock and decreased level of consciousness [18]. Despite the recommendations, it is not yet established which modality of RRT is optimal for metformin intoxication. Also, there is no consensus on the criteria for initiating and duration of extracorporeal elimination. In the opinion of some authors, patients with severe metformin intoxication are prone to rapid development and exacerbation of acidosis and cardiovascular instability and therefore advocate earlier HD initiation than recommended [12]. Pharmacokinetic properties, such as, large volume of distribution due to the rapid transition to tissue compartment, as well as, the biphasic pattern of elimination of metformin suggest that a short dialysis session would be insufficient for elimination of metformin due to a rebound phenomenon. Because it provides better drug clearance, conventional intermittent hemodialysis (IHD) should be preferred in hemodynamically stable patients. [18] Continuous renal replacement modalities such as continuous venous-venous hemofiltration (CVVH) and continuous venous-venous hemodafiltration (CVVHDF) are applicable in hemodynamically unstable patients, because they provide adequate volume repletion that is of major importance [19]. The metformin clearance provided by these modalities is 3-4 times lower than the clearance achieved by conventional HD [18]. Because of the rebound phenomenon and the increase in metformin after continuous renal replacement modalities, many authors suggest the need for simultaneous or additional prolonged IHD in cases of severe metformin poisoning [12, 20]. But the cases described by these authors have in common that they both had metformin poisoning and previous history of diabetes, a longer previous use of metformin, and one of them had a third stage of renal disease, explaining the greater volume of metformin distribution, more pronounced rebound phenomenon and the need for prolonged RRT.

We presented a case of severe metformin intoxication in a previously healthy non-diabetic young woman, with profound acidosis at pH 6.778, a high anion gap of 39.8 mmol / L and a high lactate level of 18 mmol / L. Such features usually correspond to high mortality, but with appropriate treatment the patient's condition has improved. Initial non-oliguric renal failure responded well to volumetric

replacement with crystalloid solutions. Hypotension was rapidly regulated by dopamine administration, with no further significant circulatory instability. Shortly after admission, a 2.5 h conventional bicarbonate HD was performed, along with the parenteral administration of sodium bicarbonate, which led to a gradual improvement of acidosis and lactate reduction. Determination of blood metformin levels was not available in our institution, however, lactate levels and acid-base status after HD improved, as well as the clinical signs, and no additional HD was required. Our explanation for the above is the fact the patient had not previously used metformin as a therapy, primary decontamination with active charcoal - gastric lavage was timely performed and therefore the volume of distribution was lower, thus missing a significant rebound phenomenon. The patient had no other severe comorbidities, and her leukocytosis was explained as a result of metformin-induced lactic acidosis as no definitive focus of infection was found. A similar explanation that MALA was identified as a cause of leukocytosis was provided by authors who described two other cases of MALA initially treated as sepsis [11].

Successful treatment with a 2.5-hour HD session in combination with intravenous infusions of sodium bicarbonate and dopamine was also described in a patient with a prior history of diabetes intoxicated with metformin, acarbose, and glibenclamide. The patient had moderate renal dysfunction, and similar values of pH and anion gap [11]. Also, a single session of a conventional HD resulted in clinical improvement in a patient who developed symptoms of MALA one week after starting oral antidiabetic therapy. Patient had worsened renal function due to development of neurogenic bladder as a result of diabetic neuropathy, leading to metformin accumulation [11]. Contrary to our case, fatal outcome due to multi-organ failure was observed in a young and previously healthy woman after intentional poisoning with an unknown amount of metformin despite timely applied continuous venous-venous hemodialysis continued with venous-venous hemodiafiltration. In this patient, the initial lactate was 33.0 mmol / L, and hypotension continued despite dopamine and norepinephrine therapy. This patient had a higher pH and a smaller anion gap, but higher levels of lactates compared to our patient [11]. These findings support the claim that lactate levels and profound hypotension may be predictors of fatal outcome in cases of acute metformin poisoning.

Conclusion

All patients presenting with high levels of lactate and broad anion gap metabolic acidosis should be considered for metformin poisoning, even when they are not diabetic. In intentional acute severe poisoning with metformin, RRT should be started as soon as possible to prevent rapid exacerbation of acidosis, regardless of the levels of pH and lactates. The choice of modality and duration of renal replacement therapy should be individually adjusted according to the patient's condition. A single session of conventional bicarbonate HD, if timely initiated together with parenteral administration of bicarbonates, may be sufficient to correct lactate and eliminate metformin in hemodynamically stable patients, even in severe metformin poisoning.

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