Lactate Acidosis Following a Metformin Poisoning: Which Elimination Therapy to use in Case of Haemodynamic Instability? A Case Report

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Abstract

Background: Metformin, a widespread used oral antidiabetic drug, is known for causing potential life threatening metabolic acidosis following accidental or intentional overdose. We report two cases of severe lactate acidosis with hemodynamic instability that responded poorly to intermittent dialysis as the recommended first choice elimination technique.

Case presentation: Two adult female patients presented with a similar accidental metformin intoxication at the emergency department due to acute kidney injury following dehydration. Arterial blood gas analysis showed a profound lactate acidosis, and in both patients a continuous infusion with norepinephrine was initiated. Intermittent dialysis was commenced, but severe metabolic acidosis persisted. In the first case, intermittent dialysis was replaced by continuous venovenous haemofiltration (CVVH). A gradual recovery of the metabolic acidosis, and normalization of the lactate levels were noticed. In the second case, a combination of veno-arterial extracorporeal membrane oxygenation and CVVH was needed due to cardiogenic shock. Lactate was also successfully cleared in this patient.

Conclusions: These two cases demonstrated haemodynamic deterioration and poor lactate clearance during intermittent dialysis. Therefore, in haemodynamically unstable patients due to metformin poisoning, CVVH should be considered as a first choice elimination technique.

Keywords: Metformin poisoning; Lactate; Elimination therapy

Abbreviations: CVVH: Continuous Venovenous Haemofiltration; GCS: Glasgow Coma Scale; IV: Intravenous; ED: Emergency Department; AKI: Acute Kidney Injury; ECG: Electrocardiogram; ICU: Intensive Care Unit; VA-ECMO: Veno-Arterial Extracorporal Membrane Oxygenation; ExTRIP: Extracorporeal Treatments in Poisoning

Background

Metformin is a widespread used oral antidiabetic drug. Following accidental or intentional overdose, the drug is known for causing potential life threatening metabolic acidosis [1]. A recent publication of an expert group suggested that intermittent dialysis is the first choice of elimination therapy, and considered continuous venovenous haemofiltration as an acceptable alternative [2].

We present two cases that may indicate that specifically in haemodynamic unstable patients with a severe metabolic acidosis due to metformin poisoning, continuous haemofiltration is a better therapeutic option to reach sufficient lactate and metformin elimination.

Case Presentation 1

Our medical emergency team was called to a 62-year old female with decreased consciousness. She was known with hypertension (R/ amlodipine, losartan, hydrochlorothiazide), dyslipidemia (R/ rosuvastatin), gastric ulcers (R/ pantoprazole) and diabetes mellitus type II (R/ metformin, vildagliptin). The past few days, she had suffered from a pulmonary infection with repetitive vomiting. That morning, her husband noticed a decreased consciousness, sweating and signs of an unilateral facial paralysis. At arrival, our prehospital team observed a Glasgow Coma Scale (GCS) of 11/15, tachycardia, tachypnea, and normal blood...
pressure. An intravenous (IV) line was inserted, and blood glucose measurement showed a glycaemia of 34 mg/dl. 10 g of IV glucose was immediately administered, and IV fluids were started. Although the glycaemia increased to 115 mg/dl, the decreased consciousness, tachycardia, tachypnea and sweating remained. On arrival at the emergency department (ED), arterial blood gas analysis showed a profound lactate acidosis (Table 1). Supportive therapy was started with crystalloids and sodium bicarbonate (400 ml 8.4 % and 150 ml/h of 1.4 %). Lab results revealed high leucocytes, and severe acute kidney injury (AKI) (Table 1). An electrocardiogram (ECG) demonstrated atrial fibrillation. The presumed diagnosis was AKI due to repetitive vomiting in combination with continued intake of a thiazide diuretic, and secondary lactate acidosis following a decreased metformin clearance. Despite aggressive fluid administration and norepinephrine, mean arterial pressure remained low around 58 mmHg. Low flow intermittent dialysis (250 ml/min) was commenced, but did not run uneventful. After one hour, the dialysis filter needed to be replaced due to clot formation. Furthermore, poor flow was reported several times. After 3 hours of intermittent dialysis, severe metabolic acidosis persisted (Table 1). The patient was transferred to the Intensive Care Unit (ICU) where intermittent dialysis was replaced by continuous veno-venous haemofiltration (CVVH: isovolumetric, ultrafiltration rate of 33 ml/kg, blood flow 150 ml/min, transmembrane pressure of 116 mmHg). Figure 1A demonstrates the gradual recovery of the metabolic acidosis, and normalization of the lactate levels. After 40 hours of CVVH, haemofiltration was terminated. Metabolic status remained stable afterwards. There was a rapid recovery of kidney function and haemodynamic status. The patient regained a sinus rhythm, and the inflammatory parameters disappeared. After a 4-day ICU stay, the patient was discharged to a regular nursing ward. Seven days later, she was discharged home with a total recovery of the kidney function.

| Laboratory Data | Reference values | ED Admission | Pre-ID (at 3.5h) | Post-ID (at 7.5h) | Pre-CVVH (at 10h) | Post-CVVH (at 51h) | ED Admission | Pre-ID (at 9.5h) | Post-ID (at 11.5h) | Pre-CVVH (at 14h) | Post-CVVH (at 62h) |
|-----------------|-----------------|-------------|-----------------|-----------------|------------------|-------------------|-------------|-----------------|------------------|------------------|------------------|
| pH              | 7.37-7.45       | 6.68        | 6.89            | 7.17            | 7.16             | 7.54              | 6.76        | 7.21            | 7.12             | 7.34             | 7.42             |
| PaCO$_2$ (mmHg) | 32.0-45.0       | 12.7        | 15.3            | 13.2            | 10.9             | 29.9              | 11          | 43.6            | 56.7             | 18.2             | 40.8             |
| PaO$_2$ (mmHg)  | 80.0-108.0      | 153         | 127             | 137             | 118              | 70.1              | 103         | 71.9            | 49.8             | 44.7             | 96.7             |
| HCO$_3^-$ (mmol/L) | 22.0-29.0     | 1.5         | 2.9             | 4.8             | 4.1              | 25.3              | 1.7         | 17.5            | 18.5             | 10.4             | 26.5             |
| Potassium (mmol/L) | 3.5-4.5        | 5.6         | 4.5             | 4               | 4.1              | 3.2               | 6.4         | 3.8             | 4.1              | 3.3              | 3.7              |
| Glucose (mg/dL) | 80-110          | 216         | 147             | 91              | 82               | 142               | 52          | 211             | 115              | 71               | 100              |
| Lactic acid (mmol/L) | 0.5-2.2       | 22          | 28              | 22              | 24               | 0.7               | 16          | 23              | 12.7             | 18               | 1.3              |
| Anion gap (mmol/L) | 10.0-20.0      | 44.1        | 53.6            | 43.2            | 48               | 14.9              | 39.4        | 65.3            | 36.6             | 39.9             | 16.2             |
| WBC count (x10$^3$ /mL) | 4.00-10.00    | 26.16       | 35.92           | 10.23           | 17.16            | 2.56              | 5.6         |                 |                  |                  |                  |
| CRP (mg/L)      | ≤ 5.0          | 11.7        | 11.7            | 80              | 14.7             | 3.56              | 2.6         |                 |                  |                  |                  |
| Creatinine (mg/dL) | 0.51-0.95     | 10.16       | 5.35            | 1.84            | 7.39             | 3.56              | 2.6         |                 |                  |                  |                  |
| eGFR (mL/min/1.73m$^2$) | 4              | 8           | 29              | 6               | 14               | 21               |             |                 |                  |                  |                  |
| BUN (mg/dL)     | ≤ 49           | 213         | 115             | 44              | 175              | 84                | 57          |                 |                  |                  |                  |

ED = emergency department, ID = intermittent dialysis, CVVH = continuous veno-venous hemofiltration, WBC = white blood cell, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, BUN = blood urea nitrogen.

Table 1: Serial laboratory results during hospital stay.
Case presentation 2

A 49-year old female was brought by ambulance to the ED of a regional hospital. She was known with autism, Crohn’s disease and diabetes type II (R/ vildagliptine, gliclazide, metformin). She had felt unwell the previous days and had vomited frequently. At the ED, she showed a decreased consciousness (GCS 12/15), tachypnea, tachycardia, and diaphoresis. Clinical exam revealed diffuse tenderness of the abdomen. Arterial blood gas analysis showed a severe lactate acidosis and hypoglycaemia. In addition, a severe AKI was detected (Table 1). IV fluid therapy with crystalloids, hypertonic glucose 50 % and sodium bicarbonate 8,4 % was initiated. A chest x-ray suggested pulmonary oedema.

The presumed diagnosis was prerenal AKI due to repetitive vomiting, with secondary metformin poisoning and subsequent lactate acidosis. Given the fact that the regional hospital lacked dialysis facilities, supportive therapy was continued. However, the clinical condition worsened and the patient became haemodynamically unstable. She was intubated and mechanically ventilated, and a continuous infusion with norepinephrine was initiated. The patient developed a more profound metabolic acidosis with lactate concentrations up to 29 mg/dl (Figure 1B).

Figure 1: Evolution of serum lactic acid levels and pH during the hours after admission to the emergency department. Figure 1A: case 1. Figure 1B: case 2. ID = intermittent dialysis, ECMO = extracorporeal membrane oxygenation, CVVH = continuous veno-venous hemofiltration.
Eight hours after initial presentation, the patient was transferred to our hospital for dialysis. Upon arrival at our ED, intermittent dialysis was started immediately. However, she experienced a further haemodynamic decline, for which a vasopressin drip was started in addition to the norepinephrine drip. A cardiac ultrasound showed hypocontractility of the left ventricle. A chest x-ray demonstrated bilateral diffuse infiltrates suggestive of pulmonary oedema. Based on this clinical evolution, intermittent dialysis was ceased and a veno-arterial extracorporeal membrane oxygenation (VA-ECMO) system was placed. Following this procedure, a high flux CVVH was installed after which lactate was successfully cleared. 24 hours after admission to the hospital, the patient could be weaned from ECMO. Subsequently, CVVH could be terminated after 48 hours. The AKI recovered further over the following days. The patient remained ventilated during 7 days, and was discharged to a regular nursing ward after 13 days of ICU stay.

Discussion and Conclusions

Metformin belongs to the biguanides, derived from the Galega officinalis plant. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [2, 3]. It is a small molecule (165 dalton), negligibly protein bound, with a rather large distribution volume (1 to 5 L/kg). Metformin is excreted unchanged in the urine [4]. Lactate acidosis is a rare (< 1/100,000 treated patients), but serious complication [1]. Due to the inhibition of gluconeogenesis, pyruvate is no longer converted to glucose, but is further metabolized to lactate. In addition, metformin inhibits oxidative phosphorylation, leading to an anaerobic metabolism [5].

In 2015, a systematic review of the Extracorporeal Treatments in Poisoning (ExTRIP) group formulated a 1D (strongly recommended – very low evidence) classification for the use of intermittent dialysis as the first choice therapy as renal replacement therapy in case of metformin poisoning. In the event of unavailability of intermittent dialysis, CVVH was considered a good and valid alternative [2]. In case of metformin poisoning, haemodynamic instability is mainly caused by the severe metabolic acidosis. Therefore, the ExTRIP working group stated that rapid acidosis normalisation by using intermittent dialysis was more important than the risk of additional haemodynamic instability.

However, our 2 cases demonstrated haemodynamic deterioration and poor lactate clearance during intermittent dialysis. For these reasons, we decided to switch to CVVH as alternative renal replacement therapy. Thereafter, we observed an efficient lactate clearance and a quick clinical recovery of the patients. Some case reports published after the publication of the ExTRIP working group also considered haemodynamic instability as an important reason to prefer CVVH [7-9].

In conclusion, our 2 presented cases provide further arguments that in haemodynamically unstable patients due to metformin poisoning, CVVH should be considered as a first choice elimination technique.

Declarations

Ethics Approval and Consent to Participate: The study was approved by the hospital Ethics Committee. Given the observational design of the study, informed consent was waived.

Consent for Publication: Given the fact that informed consent was waived, this included the consent for publication.

Availability of Data and Materials: All data generated or analysed during this study are included in this published article.

Competing Interests: The authors declare that they have no competing interests.

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Authors’ Contributions

LH, MS and SV provided care for the patients in the emergency department. LH and JC searched the medical files and interpreted the patient data. LH and JC wrote the article which was critically reviewed by MS and SV. All authors read and approved the final manuscript and its submission for the Annals of Case Reports.

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