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Acid-Base and Electrolyte Teaching Case

# Treatment of Metformin Intoxication Complicated by Lactic Acidosis and Acute Kidney Injury: The Role of Prolonged Intermittent Hemodialysis

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Metformin intoxication with lactic acidosis, a potentially lethal condition, may develop in diabetic patients when the drug dose is inappropriate and/or its clearance is reduced. Diagnosis and therapy may be delayed due to nonspecific symptoms at presentation, with severe anion gap metabolic acidosis and elevated serum creatinine values being the most prominent laboratory findings. Confirmation requires measurement of serum metformin by high-performance liquid chromatography–tandem mass spectrometry, but this technique is available only at specialized institutions and cannot be relied on as a guide to immediate treatment. Thus, based on strong clinical suspicion, renal replacement therapy must be started promptly to achieve efficient drug clearance and correct the metabolic acidosis. However, because metformin accumulates in the intracellular compartment with prolonged treatment, a rebound in serum concentrations due to redistribution is expected at the end of dialysis. We report a case of metformin intoxication, severe lactic acidosis, and acute kidney injury in a diabetic patient with pre-existing chronic kidney disease stage 3, treated effectively with sustained low-efficiency dialysis. We discuss the pathophysiology, differential diagnosis, and treatment options and highlight specific pharmacokinetic issues that should be considered in selecting the appropriate modality of renal replacement therapy.
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***INDEX WORDS:*** Acute intoxication; metformin intoxication; acute kidney injury (AKI); lactic acidosis; diabetes; metformin-associated lactic acidosis (MALA); kidney function; drug clearance; renal replacement therapy (RRT); sustained low-efficiency dialysis (SLED); chronic kidney disease (CKD); drug safety.

## INTRODUCTION

Metformin is a biguanide currently regarded as a first-line glucose-lowering agent for type 2 diabetes mellitus; it is inexpensive, is safe, has low risk for hypoglycemia, may promote moderate weight loss, and is associated with decreased incidence of macrovascular complications.[1,2] Metformin also has pleiotropic vasoprotective effects, which include improved endothelial function, suppression of glycation and oxidative stress, and stimulation of fibrinolysis, among others.[3]

Because metformin inhibits mitochondrial respiration in insulin-dependent tissues and also activates anaerobic glucose metabolism in the intestine, accumulation of this drug can increase serum lactate concentrations.[3,4] Intentional metformin overdose can directly induce lactic acidosis,[5,6] although this is not always the case.[7] However, more frequently, lactic acidosis is precipitated by metformin accumulation when its clearance is reduced, as in diabetic patients with chronic kidney disease (CKD), during episodes of acute kidney injury (AKI), or with liver failure caused by shock states and/or volume depletion. This condition is termed metformin-associated lactic acidosis (MALA).[3,4] Although its incidence is less than 10 events/100,000 patient-years of exposure,[3,8-11] MALA is a highly feared complication: a 30% mortality rate has been reported in the most severe cases.[11]

We report a case of MALA due to metformin accumulation in a diabetic patient with AKI on CKD stage 3 and discuss the pathophysiology, diagnosis, and treatment options. We focus specifically on relevant pharmacokinetic issues that should guide the choice of the most appropriate modality of emergency renal replacement therapy (RRT).

## CASE REPORT

### Clinical History and Initial Laboratory Data

A 76-year-old man with type 2 diabetes, CKD stage 3 (previous serum creatinine [Scr] concentration, 1.8 mg/dL, corresponding to estimated glomerular filtration rate [eGFR] of 36 mL/min/1.73 $m^2$ as calculated using the CKD-EPI equation), and ischemic cardiomyopathy (ejection fraction, 20%-25%) presented with a 48-hour history of vomiting, abdominal pain, hypotension, and oliguria after uncomplicated day surgery for an inguinal hernia 3 days

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earlier. His usual medications included aspirin, 100 mg; ramipril, 7.5 mg; bisoprolol, 2.5 mg; furosemide, 25 mg, twice daily; metformin, 1,000 mg, 3 times daily; and glimepiride, 1 mg. Physical examination revealed an oliguric 72-kg man in moderate respiratory distress, with cold extremities and a large hematoma of the abdominal wall extending to the scrotum and left thigh. Blood pressure was 90/50 mm Hg while on dopamine, 8 μg/kg/min; pulse rate, 56 beats/min; respirations, 32 breaths/min; peripheral oxygen saturation, 98% on 50% oxygen; and tympanic temperature, 35.5°C. Initial laboratory workup showed a severe anion gap metabolic acidosis with hyperlactatemia and AKI on CKD (Table 1). Other routine serum values and urine toxicology tests were unremarkable.

In the renal intensive care unit, hemodynamics were supported with 1.4% bicarbonate and norepinephrine, 0.20 μg/kg/min. Empirical antibiotic therapy was started with ceftazidime and levofloxacin. A 12-Fr central venous catheter was inserted in the right internal jugular vein, and RRT was started with an AK 200ultra machine (Gambro/Baxter) and a 1.8 $m^2$ polysulfone F8 HPS filter (Fresenius). A 16-hour sustained low-efficiency dialysis (SLED) session with regional citrate anticoagulation[12] was planned (bicarbonate [32 mmol/L]; blood flow rate, 200 mL/min; dialysis fluid rate, 300 mL/min; countercurrent flow direction; and +2.5-kg body weight change).

## Additional Investigations

Blood samples were collected during the SLED session, as well as 1 and 4 hours thereafter; the most relevant intradialytic acid-base and hemodynamic parameters were also recorded. Serum metformin was measured subsequently by high-performance liquid chromatography–tandem mass spectrometry. Metformin levels at the initiation of SLED were in the potentially lethal range and decreased rapidly within 8 hours of treatment; however, a moderate rebound in serum metformin levels was observed 4 hours after SLED was terminated (Fig 1).

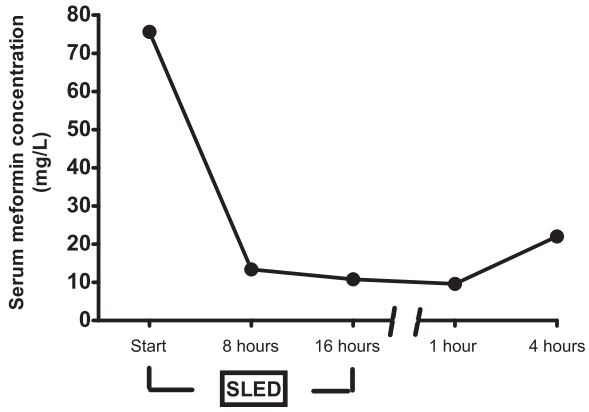


**Figure 1.** Time course of plasma metformin concentration during and after the sustained low-efficiency dialysis (SLED) session. Note the rebound 4 hours after the end of the SLED session. The therapeutic range for metformin is 1 to 3 mg/L.

## Diagnosis

Severe lactic acidosis likely from metformin intoxication secondary to overprescription in a patient with type 2 diabetes mellitus, pre-existing CKD stage 3b, and hypovolemic AKI.

## Clinical Follow-up

Blood pressure gradually increased during SLED, and norepinephrine dosage was tapered and eventually discontinued by the end of treatment. Acid-base parameters at the end of SLED returned to the normal range (Table 1). Urinary output rapidly increased within the 48 hours after SLED, and no further dialysis was required.

Kidney function displayed partial recovery during the hospitalization, with an Scr concentration at discharge of 2.5 mg/dL

**Table 1.** Laboratory Data During and After the SLED Session

| Laboratory Data | Hospital Admission | SLED Start | Hour 8 of SLED | SLED End (at 16 h) | 1 h Post-SLED | 4 h Post-SLED |
|---|---|---|---|---|---|---|
| pH | 6.96 | 6.92 | 7.36 | 7.39 | 7.38 | 7.37 |
| $Paco_2$, mm Hg | 20.2 | 20.8 | 34.0 | 35.9 | 35.8 | 35.4 |
| $Pao_2$, mm Hg | 100 | 100 | 100 | 71.8 | 74.3 | 75.9 |
| $HCO_3^-$, mmol/L | 6.1 | 5.9 | 20.7 | 26.6 | 25.8 | 24.2 |
| Lactate, mmol/L | 16 | 17 | 4.3 | 2.0 | 1.7 | 1.5 |
| AG, mmol/L | 26 | 27 | | 6 | 6 | 8 |
| Blood glucose, mg/dL | 211 | 221 | 110 | 102 | 101 | 105 |
| SUN, mg/dL | 105 | 98 | 29 | NA | NA | NA |
| Scr, mg/dL | 8.1 | 8.1 | 2.4 | NA | NA | NA |
| eGFR, mL/min/1.73 $m^2$ | 6 | 6 | 25 | | | |
| Potassium, mmol/L | 6.0 | 6.1 | 5.0 | 4.5 | | |
| Calcium, mEq/L | 2.41 | 2.40 | 2.18 | 2.16 | 2.16 | 2.18 |
| WBC count, $\times 10^3$/mL | 11.8 | 11.9 | 8.5 | NA | NA | NA |
| Hb, g/dL | 11.6 | 11.7 | 10.5 | 10.9 | 10.7 | 10.6 |
| Platelet count, $\times 10^3$/mL | 147 | 147 | 132 | NA | NA | NA |
| CRP, mg/L | >250 | >250 | NA | NA | NA | NA |
| Prothrombin time ratio | 1.07 | 1.06 | NA | NA | NA | NA |
| Activated clotting time, s | NA | 110 | NA | NA | NA | NA |

*Note:* Conversion factors for units: Scr in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357; calcium ion in mEq/L to mmol/L, ×0.5; blood glucose in mg/dL to mmol/L, ×0.05551.

Reported arterial plasma bicarbonate values are expressed as standard bicarbonate (ie, the concentration of hydrogen carbonate in the plasma from blood which is equilibrated with a gas mixture with *p*COB2B = 5.33 kPa [40 mmHg] and *p*OB2B ≥ 13.33 kPa [100 mmHg) at 37°PC], as given by the output of a blood gas analyzer ABL 900 Flex, Radiometer.

Abbreviations: AG, anion gap; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; NA, not available; Scr, serum creatinine; SLED, sustained low-efficiency dialysis; SUN, serum urea nitrogen; WBC, white blood cell.