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Successful treatment of metformin and rodenticide intoxication with prolonged hemodialysis and methylene blue: A case report

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ABSTRACT

Metformin is a first-line treatment for diabetes mellitus. In cases of suicidal overdose or chronic accumulation, lactic acidosis may develop and, if untreated, can be fatal. Renal replacement therapy plays a key role in reversing the condition. Refractory hypotension may be encountered both in the presentation of intoxication cases and as a complication of renal replacement therapy. Methylene blue is recommended to improve blood pressure in such cases. A 25-year-old male presented to the emergency department after ingesting a high dose of metformin and around 20 g of rodenticide in a suicide attempt. On admission, his condition was poor, tachycardic, with a blood pressure of 98/42 mmHg. Blood gas analysis revealed a pH of 7.015, pCO2 22.6 mmHg, pO2 64.4 mmHg, base excess −23.4 mmol/L, HCO3 5.5 mmol/L, and lactate 23 mmol/L. Conventional treatments failed, so intermittent hemodialysis was performed. Methylene blue was given for persistent hypotension, stabilizing his hemodynamics. The rodenticide contained difenacoum, a superwarfarin, but laboratory results showed no need for intervention, and no bleeding signs were observed. Blood gas values normalized during his stay in the toxicology unit. After failing a weaning trial, he tested positive for COVID-19 and was transferred to the ICU. After 23 days of care in the emergency and ICU, he was discharged in good health. Lactic acidosis from metformin overdose is a serious condition, and renal replacement therapy can significantly improve survival. Methylene blue may be beneficial in refractory shock, but further randomized controlled trials are needed to clarify its role, especially in cases with combined toxic exposures like rodenticides.

1. Introduction

Metformin is an agent derived from the Galega officinalis plant and is frequently used in the treatment of non-insulin-dependent diabetes mellitus. The therapeutic plasma concentration of metformin ranges from 0.1 mg/L to 4 mg/L, with a recommended daily dose of 20 mg/kg [1]. In cases of high-dose metformin ingestion with suicidal intent, renal failure and lactic acidosis are commonly observed. Since there is no specific antidote, hemodialysis is the mainstay of treatment, alongside supportive care [2]. Hypotension can develop either as a result of intoxication or as an unwanted side effect of renal replacement therapy. At this point, methylene blue, which is not yet part of routine treatment, can be considered in cases with refractory shock [3,4].

As with all drug intoxication cases, clinicians must always assess the possibility of multiple toxic substance exposures. In this case, along with metformin ingestion, the patient also consumed 20 g of rodenticide (Tibtrap brand rodenticide paste). Due to the presence of different active ingredients, the clinical presentation of rodenticide toxicity can vary significantly. Our case involved difenacoum, a superwarfarin or long-acting anticoagulant that is 100 times more potent than warfarin. It inhibits the production of vitamin K-dependent clotting factors II, VII, IX, and X, leading to a tendency for bleeding. Treatment includes vitamin K supplementation, and in cases of active bleeding, blood product replacement is applied [5,6].

This case describes a patient who presented to our clinic after ingesting rodenticide and a toxic dose of metformin. It highlights the potential benefits of early initiation of extracorporeal treatment and the use of methylene blue in refractory shock to reduce mortality.

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2. Case report

A 25-year-old male patient was admitted due to drug intoxication. Information obtained from relatives revealed that approximately 3 hours prior to admission, the patient had ingested 98 tablets of Glifor (Metformin) 1000 mg and around 20 g of rodenticide containing 0.005 % difenacoum, with suicidal intent.

Physical examination: The patient's general condition was poor, with fluctuating consciousness. He presented with a delirium state, a Glasgow Coma Scale score of 13, arterial blood pressure of 98/42 mm Hg, pulse rate of 132 beats per minute, body temperature of 36.4 degrees Celsius, and oxygen saturation of 96 %. No significant pathology was found in other system examinations. Electrocardiogram (ECG) showed sinus tachycardia. Laboratory parameters outside the normal range were: creatinine 1.7 mg/dL, International Normalised Ratio (INR) 1.67, pH 7.015, pCO2 22.6 mmHg, pO2 64.4 mmHg, base excess −23.4 mmol/L, HCO3 5.5 mmol/L, and lactate 23 mmol/L (Table 1). Metformin blood levels could not be measured in our clinic, and the toxicology panel was reported as negative. A non-contrast brain computed tomography (CT) was performed to rule out bleeding-induced changes in consciousness and was found to be normal.

After airway, breathing, and circulation stabilization, 50 g of activated charcoal was administered orally. A urinary catheter was placed to monitor fluid resuscitation. Since the effects of the rodenticide containing difenacoum may appear in 3–5 days, 10 mg of vitamin K was administered intravenously via slow infusion as a precaution to the patient, who did not have active bleeding. As the patient's acidosis deepened and consciousness worsened, he was intubated. Sodium bicarbonate was administered at a rapid dose of 1 meq/kg, followed by a slow infusion of 0.5 meq/kg/h for 6 hours. Intermittent hemodialysis was initiated via the right subclavian vein. In the patient whose blood pressure did not improve, norepinephrine at 0.2 mcg/kg/min and dopamine at 10 mcg/kg/min were initiated, with doses increased to target a minimum mean arterial pressure of 65 mm Hg. For hypotension that did not respond to these measures, methylene blue was administered at a loading dose of 1.5 mg/kg in 500 ml of 5 % dextrose over 30 minutes, followed by an infusion of 1 mg/kg/h for 12 hours. Hemodialysis, initiated in the 3rd hour after admission and applied intermittently for a total of 20 hours, was terminated without complications as the patient's blood pressure and arterial blood gas normalized. Although laboratory and ventilator parameters improved after 48 hours, an extubation attempt was unsuccessful (Fig. 1). The patient, with infiltrates on chest X-ray and a positive COVID-19 PCR result, was admitted to the intensive care unit. After 3 days in the emergency toxicology unit and 20 days in intensive care, the patient was discharged in good health.

Table 1
Values at Admission and Before ICU Transfer (3 Days Later).

Parameter	Admission	ICU transfer	Normal range
Glucose	153	156	70–100 mg/dL
CRP	12.0	**100.0**	0–5 mg/L
Creatinine	**1.7**	**1.36**	0.67–1.17 mg/dL
WBC	9160	9500	4–10 10^3/uL
Hemoglobin	13.5	11	13.2–16.6 g/dL
Platelet	216	**89**	150–450 10^3/uL
AST/ALT	34/31	**267/122**	10–40/7–56 U/L
Albumin	43	40	35–50 g/L
Na	130	135	135–145 mmol/L
K	4	4.1	3.5–5.1 mmol/L
Cl	97	102	98–106 mmol/L
Ca	8.8	9.5	8.5–10.5 mg/dL
Urea	17.0	27.0	13–47 mg/dL
Total Bilirubin	0.54	0.59	0.2–1.2 mg/dL
Direct Bilirubin	0.11	0.1	0.1–0.3 mg/dL
INR	**1.67**	**1.33**	0.8–1.2
pH	**7.015**	7.400	7.35–7.45
pCO2	**22.6**	**46.5**	35–45 mmHg
BE	**−23.4**	**3.7**	−2 to +2 mEq/L
HCO3	**5.5**	27.4	22–28 mEq/L
pO2	**64.4**	**211**	75–100 mmHg
Lactate	**23**	**2**	0.5–1.0 mmol/L

CRP: C-Reactive Protein, WBC: Wight Blood Cell, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, INR: International Normalised Ratio, BE: Base excess.

3. Discussion

Although metformin-associated lactic acidosis is a well-known condition in acute poisoning cases, we identified two aspects that make this case unique: the concurrent ingestion of rodenticide and the use of methylene blue in the treatment of refractory hypotension. While measuring serum metformin levels is not mandatory for diagnosis and treatment, it can provide valuable guidance.

Typically, lactic acidosis is expected as an indicator of tissue hypoperfusion, but it can also occur as a result of drug-induced reduced lactate metabolism (Type B lactic acidosis) [1]. In addition to fluid resuscitation and supportive therapies, hemodialysis is required for primary management [7]. The defined indications for hemodialysis include a pH less than 7.20, lactate levels above 10, altered mental status, shock, and failure of supportive treatment attempts [2]. This case met all the indications, and hemodialysis was initiated as early as possible. However, in cases involving hypotension, continuous renal replacement therapy would be a more appropriate approach, but we were unable to apply this in our clinic [8,9]. As described in the literature, hemodialysis is the most effective treatment for metformin-associated lactic acidosis, and in our patient, blood gas follow-ups showed dramatic improvement.

Despite adequate fluid resuscitation and at least 6 hours of vasopressor administration, the patient's hypotensive course persisted, leading to the application of methylene blue. Pasin et al. in 2013, through a meta-analysis, demonstrated that methylene blue could increase arterial blood pressure without having a negative effect on survival [10]. Although not a widely used treatment modality, we observed a positive response in this case. While not yet definitively recommended, numerous cases support the use of methylene blue in refractory shock [3, 4, 11]. Katlan describes a similar case where methylene blue was effective in managing refractory hypotension in a patient on continuous renal replacement therapy [12]. In our case, due to clinical limitations, we could not consider the option of continuous renal replacement therapy. However, the patient's hypotensive course prior to extracorporeal treatment spared us from the adverse hemodynamic effects of hemodialysis in this case. The improvement in mean arterial pressure during hemodialysis with methylene blue administration supports our reasoning (Fig. 2). We believe that the hemodynamic effects of methylene blue need to be better understood through randomized controlled trials.

After rodenticide ingestion, the identification of the active ingredient should be done promptly. In this case, the substance was difenacoum, which has anticoagulant properties. Due to its longer elimination and higher potency, it is known as a 'superwarfarin' or 'long-acting' anticoagulant. The lethal oral dose is reported to be between 0.12 and 0.172 mg/kg. Its effects typically begin 36–48 hours after ingestion and can last for days. For diagnosis and treatment, it is crucial to measure and normalize INR values [6]. However, the follow-up period should be extended, as the effects can persist for up to 289 days, according to the literature [13]. Fortunately, in our case, the intake amount was low, and the daily monitored INR values were within acceptable levels. During the emergency and ICU follow-up, no signs of bleeding or laboratory (INR values) abnormalities developed. However, due to the accompanying COVID infection, the ICU stay was prolonged.

The combined effect of these two toxic exposures, which we attempted to treat separately, remains uncertain. In this case, we primarily focused on the clinical presentation of metformin toxicity, which was the most prominent.

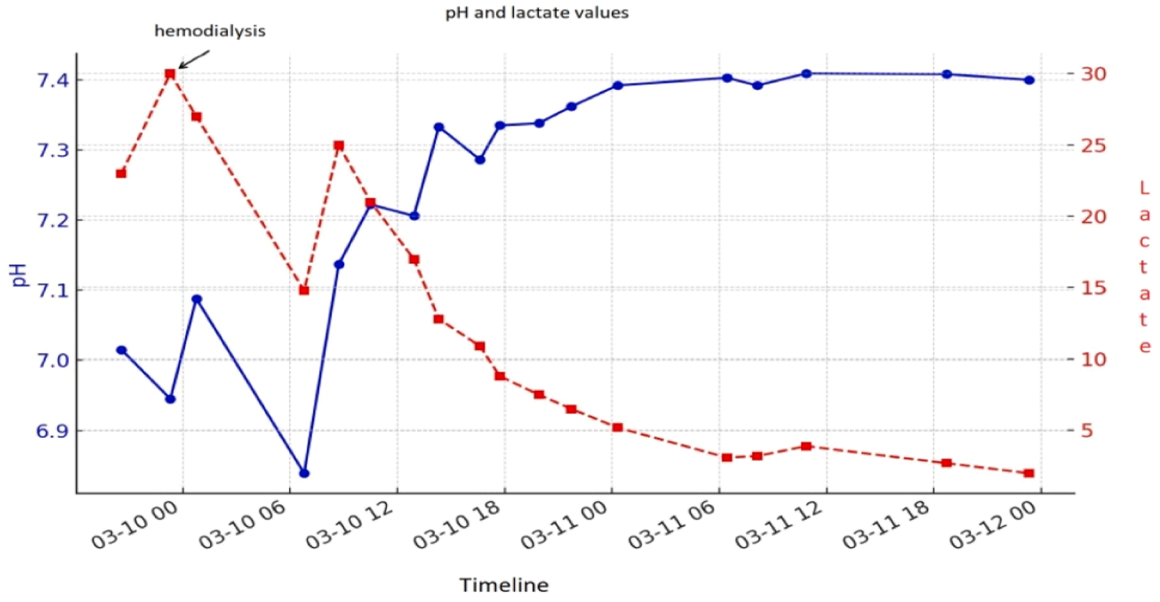

Fig. 1. : Change of pH and lactate values over time. With the initiation of hemodialysis, lactate levels are decreasing.

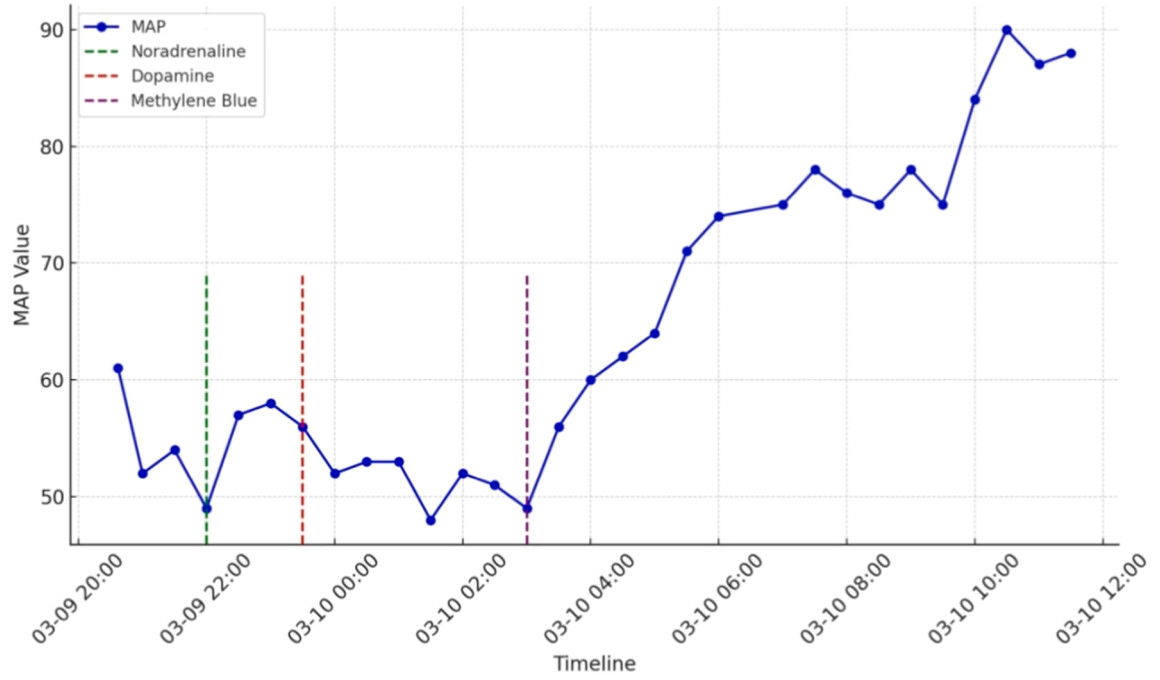

Fig. 2. : Monitoring of Mean Arterial Pressure (MAP). The positive effect of methylene blue in a patient unresponsive to norepinephrine and dopamine. Blood pressure measurement was performed non-invasively.

4. Conclusion

Prolonged hemodialysis is a crucial step in the treatment of acute metformin poisoning. Methylene blue appears to be an intriguing option for the management of refractory hypotension. The clinical impact of toxic exposure combined with rodenticide warrants further investigation.

CRediT authorship contribution statement

Mustafa Bozkurt: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration. **Mustafa SABAK:** Writing – review & editing, Validation, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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