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CASE REPORT

Successful use of methylene blue for catecholamine-refractory vasoplegic shock due to metformin intoxication: A case report and literature review

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Abstract

Background: Severe metformin intoxication can lead to lactic acidosis and vasoplegic shock, for which the optimal management strategy remains uncertain, especially in cases of severe circulatory collapse.

Case Presentation: A 45-year-old diabetic woman on metformin therapy presented with impaired consciousness and seizures. She had experienced a cardiac arrest and undergone extracorporeal cardiopulmonary resuscitation. Blood gas analysis showed severe lactic acidosis. A 71-g metformin packet was found at the patient's home, suggesting an overdose. Despite extracorporeal support and blood purification, severe lactic acidosis and hypotension persisted. Methylene blue was administered 32 h from the onset, which improved her metabolic and circulatory status. We examined her blood sample throughout the case to check the transition of metformin blood concentration.

Conclusion: Methylene blue may be beneficial for severe metformin toxicity, regardless of the blood concentration of metformin and the time since intoxication. However, further research is needed to establish its optimal use and effectiveness.

KEYWORDS
drug-related side effects and adverse reactions, metformin, methylene blue, poisoning, vasoplegia

INTRODUCTION

It is widely known that metformin overdoses can lead to severe lactic acidosis, which is called metformin-associated lactic acidosis (MALA). However, the occurrence of severe distributive shock due to vasodilation is a less frequently reported consequence of metformin overdoses.[1] We present a case of severe metformin intoxication that was treated with methylene blue (MB). This report is valuable and unique in that it describes both the change in metformin blood concentration over time and the timing of MB administration.

CASE REPORT

A 45-year-old woman, who was 165 cm tall, weighed 90 kg, with a history of diabetes mellitus and cerebral infarction, was admitted to the hospital. The woman was found in a corridor one morning. Despite being initially responsive, she subsequently became disoriented and had a convulsive seizure, prompting a call to emergency services. Before arriving at the hospital, the patient fell into pulseless electrical activity (PEA). The emergency services initiated cardiopulmonary resuscitation (CPR), secured her airway with a supraglottic device, established venous access, and administered

intravenous adrenaline. The patient was brought to the hospital with a return of spontaneous circulation (ROSC).

Upon arrival, she had a Glasgow Coma Scale score of E1VTM1, a blood pressure of 47/30 mmHg, a heart rate of 71 bpm, and an unmeasurable SpO_2 level and body temperature. After tracheal intubation, blood gas analysis revealed severe lactic acidosis with a pH of 6.757 and the following findings: HCO_3^-: 9.5 mmol/L, Glu: 529 mg/dL, and lactate: 18.0 mmol/L. Due to the patient's repeated episodes of PEA and ROSC, indicating hemodynamic instability, we performed venoarterial extracorporeal membrane oxygenation (VA-ECMO) treatment as part of extracorporeal CPR. A computed tomography (CT) scan, performed after the circulation was stabilized, did not identify a specific cause of the cardiac arrest. It was later determined that she was regularly taking 2 g/day of metformin and had ingested approximately 71 g of metformin, based on an empty medicine packet found in her home. Although she was admitted to the ICU for further treatment, her lactate level increased to the point of being unmeasurable (ABL90 FLEX system; Radiometer Medical Aps., lactate measurement limit: 0–31 mmol/L). Continuous hemodiafiltration dialysis (CHDF) was initiated at 4 h after arrival to correct the acidosis and remove the metformin. Activated charcoal was not administered. Although circulation was established by ECMO (approximately 2400 rpm, 3.5 L/min), the patient's circulatory failure persisted. She received vasoconstrictors, including a maximum dose of 0.83 γ norepinephrine, 2 U/h vasopressin, and 0.17 γ adrenaline continuously (i.e., her catecholamine index [CAI] = 100 [CAI = dopamime + dobutamine + (adrenaline + noradrenaline) × 100 μg/kg/min]). Bedside cardiac echo showed that her ejection fraction was approximately 30%. Although we did not initiate any hemodynamic monitoring device, we thought she was suffering from severe vasoplegic shock including ischemic–reperfusion response and metformin toxicity, because there was no improvement with an extremely high dose of catecholamine. We consulted a review article on metformin toxicity[2] and decided to try MB therapy. One hundred milligrams of MB was administered intravenously as a single dose (starting 32 h after onset, over 1 h) after approval from the hospital ethics committee for its off-label use. After the MB was administered, the patient's blood pressure improved and her catecholamine requirement decreased. In addition, her lactate levels became measurable and began to decrease over time (Figure 1). In this case, the metformin levels in her blood and dialysate waste were measured over time. These measurements showed that her blood concentration of metformin immediately on arrival was 130 mcg/mL, and the approximate half-life of the drug was 5–9 h (Figure 2). At the time of the MB administration, the patient had already experienced fatal circulatory failure and metabolic acidosis, as described above, but her blood concentration of metformin at this time was estimated to be approximately 10 mcg/mL, a significant decrease from the peak concentration. On the 4th day of her illness, a cranial CT scan revealed hypoxic encephalopathy, indicating a poor neurological prognosis. She was weaned from ECMO on the 6th day, while CHDF continued to the end and was discharged dead on the 10th day. Her blood culture subsequently proved negative, supporting that her refractory shock was mainly due to metformin intoxication.

DISCUSSION

Treatment for metformin intoxication involves drug elimination through hemodiafiltration and supportive care. Metformin, a non-metabolized drug with a 5-h half-life, is excreted unchanged in urine. However, it is widely distributed in tissues, including the intestines, liver, and kidneys.[3]

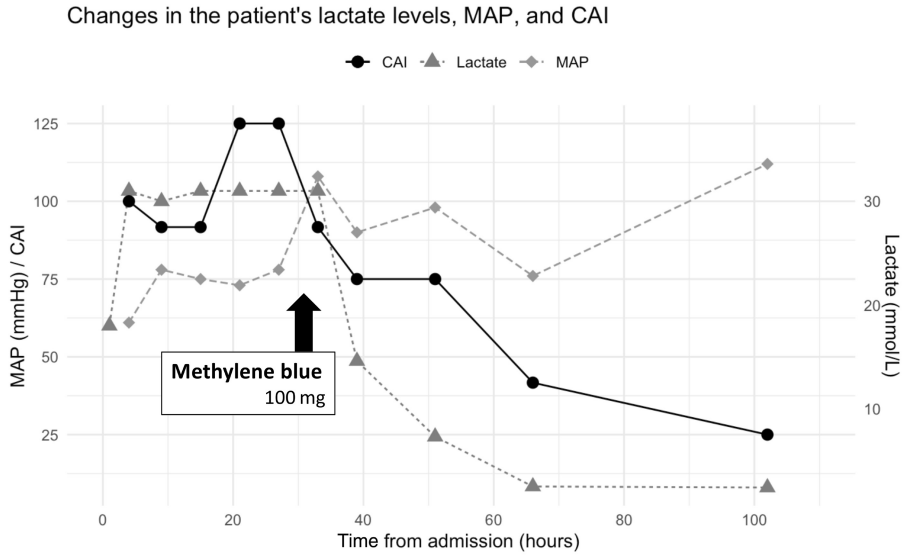

FIGURE 1 Changes in the patient's lactate levels, MAP, and CAI. CAI, catecholamine index; MAP, mean arterial pressure. After the administration of methylene blue, there was an immediate increase in the patient's blood pressure, and her catecholamine index also showed a decreasing trend. In addition, the patient's lactate levels, which were initially unmeasurable, became measurable and demonstrated a decreasing trend over time.

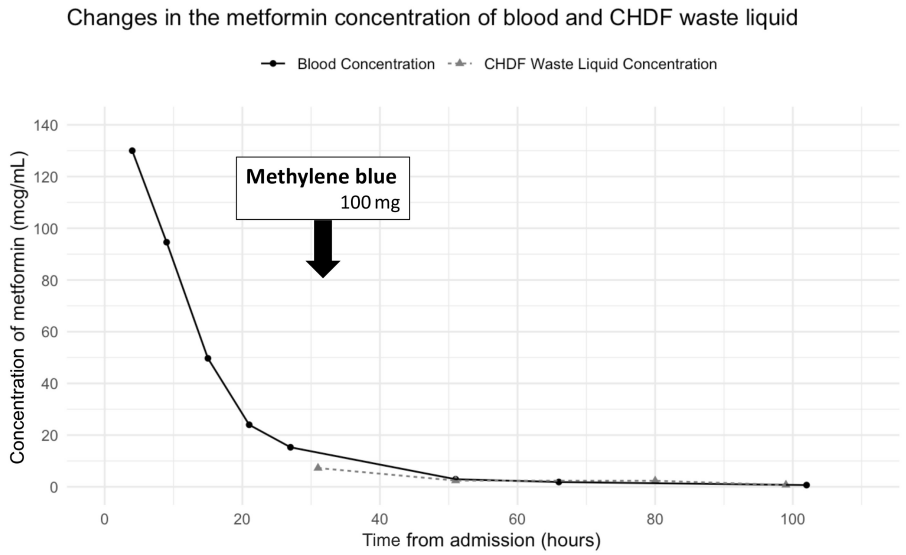

FIGURE 2 Changes in the metformin concentrations of blood and CHDF waste liquid. CHDF, continuous hemodiafiltration. The temporal changes in the metformin concentrations of blood and the waste dialysate fluid are presented. The blood concentration consistently showed a decreasing trend, and there was no significant difference between the metformin concentrations of blood and waste dialysate fluid, suggesting efficient removal of the drug through dialysis. On the contrary, the blood concentration of metformin had significantly decreased by the time methylene blue was administered.

Therefore, high blood levels can help to diagnose metformin toxicity, but the severity of the condition cannot be determined based on blood metformin levels alone. We used MB to treat metformin poisoning due to its theoretical efficacy against both MALA and severe hypotension, which are the toxic mechanisms in metformin intoxication.

MALA

Metformin interferes with oxidative phosphorylation by inhibiting complex I, leading to incomplete electron transfer.[4] Inactivation of complex I partially inhibits electron transport to Coenzyme Q, resulting in hydrogen ions not being adequately processed within the mitochondria. Thus, excessive accumulation of metformin can disturb the intracellular electron transfer system and the REDOX reaction balance, leading to impaired lactate excretion and glucose synthesis from lactic acid, and resulting in metabolic acidosis. MB can counteract this by acting as an electron exchange carrier, restoring oxidative phosphorylation and the citric acid cycle. More precisely, MB acts as an electron carrier when it accepts electrons from NADH and then passes them to ubiquinone or cytochrome c. This means that MB revives the oxidative phosphorylation and the citric acid cycle.

Hypotension

Nitric oxide (NO) is a well-known mediator of vasodilation in blood vessels and is synthesized from L-Arginine and oxygen by the endothelial nitric oxide synthase (eNOS). When NO binds to guanylate cyclase (GC), a receptor for NO,[5] GC converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), a messenger that relaxes vascular smooth muscle and causes vasodilation. Thus, NO performs its vasodilator effect via GC. Metformin activates eNOS, leading to increased NO production. Excessive NO production can cause severe vasoplegic shock through reduced vascular resistance and vasoconstrictor responsiveness in severe metformin intoxication. MB inhibits GC and related pathways, helping to treat severe hypotension caused by metformin toxicity.

Although there is some theoretical support for MB therapy for metformin poisoning, its clinical utility and the optimal administration protocols are not well established. A PubMed search for "metformin, methylene blue" only yielded four case reports in English[6–9] (Table 1). In those cases, MB was mainly used to save patients in severe vasoplegic shock that were unresponsive to extreme catecholamine doses. Immediately after the administration of MB, their blood pressure increased, and their catecholamine requirements were significantly reduced. While the optimal dosage of MB for metformin poisoning is currently unclear, most patients received an initial dose of 2 mg/kg, likely because the general recommendation for treating methemoglobinemia is a single 1–2 mg/kg dose.[10] Although some received a sustained or second dose, it must be noted that high doses (up to 7 mg/kg) can reduce abdominal blood flow.[11] The blood metformin concentrations in two of the above-mentioned cases[8,9] were four to five times higher than that of ours, suggesting that blood metformin levels may not be correlated with disease severity. Tallman et al. also administered MB to their patient for severe vasoplegic shock and reported a subsequent need for VA-ECMO, but concurrent trazodone intoxication with alpha-receptor blocking effects may have interfered with the effectiveness of MB in their case.[8] Workum et al.[9] detailed MB administration in a case involving a concurrent

TABLE 1 Literature review on the use of methylene blue for metformin intoxication.

Authors	Details of patient	Dose	Metformin blood concentration	Co-intoxication	Labs
Plumb et al.[5]	66-year-old female | toxicity due to septic AKI	2 g/day	N/A	10 mg/day ramipril	pH 6.57, base excess: −35.6 mEq/L, lactate: 17.0 mmol/L
Graham et al.[6]	40-year-old male | overdose	35.0 g	N/A	2.1 g gliclazide	Glu: 38 mg/dL, pH 6.88, HCO_3^-: 4 mmol/L, $PaCO_2$: 23 mmHg, lactate: 29.0 mmol/L
Tallman et al.[7]	36-year-old male | overdose	Unknown	678 mcg/mL	Trazodone (unknown dose)	pH 7.05, $PaCO_2$: 19 mmHg, lactate: 33.8 mmol/L (on CRRT)
Workum et al.[8]	55-year-old female | overdose	82.5 g	622.9 mcg/mL	10 g acetaminophen, 420 mg semaglutide	pH 7.19, HCO_3^-: 16 mmol/L, $PaCO_2$: 42 mmHg, lactate: 9.5 mmol/L

Pressor and interventions	Methylene blue dosage	Administration time from admission	Recovery from vasoplegia	Adverse event	Status
ACLS for pulseless electrical activity for one cycle, calcium gluconate, sodium bicarbonate, hydrocortisone, CHDF, 1.55 mcg/kg/min noradrenaline	2 mg/kg followed by 2 mg/kg/h for 12 h	16 h	Yes	None	Survived
CRRT, IHD, hydrocortisone, empiric antibiotics, proning; 1.7 mcg/kg/min noradrenalin, 3.6 units/h vasopressin	2 mg/kg followed by 0.25 mg/kg/h for 20 h	13 h	Yes	None	Survived
CRRT, VA-ECMO; noradrenaline, adrenaline, vasopressin, phenylephrine (dose not described)	2 mg/kg	<19 h (not clearly described)	Partial	None	Survived
CRRT, hydrocortisone; 1.2 mcg/kg/min noradrenalin, 1.8 units/h vasopressin	2 mg/kg twice	33 h	Yes	Liver necrosis	Deceased

Abbreviations: ACLS, advanced cardiac life support; AKI, acute kidney injury; CHDF, continuous hemodiafiltration dialysis; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

hepatotoxic drug overdose, which resulted in liver necrosis. Thus, MB may be life-saving in patients with severe metformin toxicity when other options are unavailable, but excessive doses should be avoided.

We have gained important insights from this case that MB administration significantly improved the patient's condition, even when metformin levels had substantially decreased. MB was administered when the patient's blood metformin concentration had dropped to 10%–15% of its peak level (Figure 2). Nevertheless, the patient's lactate levels appeared to decrease, as did her CAI, whereas her mean arterial pressure increased (Figure 1). Although we cannot rule out the possibility that the patient's condition simply took its natural course, Workum et al. also reported that the administration of MB 33 h after arrival, combined with early blood purification therapy, effectively countered the toxic effects of metformin.[9] This suggests the potential efficacy of MB in combating the toxic effects of metformin, regardless of the time elapsed since the ingestion of metformin, and even when the patient's metformin blood concentration is expected to have decreased, as long as metabolic disturbances and circulatory insufficiency persist. Nevertheless, this is not beyond our theory, as we could not find any related articles in a PubMed search. In the future, more cases are needed to validate the effectiveness of MB administration against metformin toxicity.

CONCLUSION

It was suggested that MB may be useful in treating symptoms of metformin intoxication, both MALA and vasoplegic shock, regardless of the blood concentration of metformin or the time elapsed after the onset of symptoms.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All of the data collected for this study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Approval of the research protocol: N/A.
Informed consent: By signing the informed consent document, the patient's family has given permission for the details of this case report to be published.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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