A 72-year-old woman with a history of type 2 diabetes mellitus was brought to the ER with metformin-associated lactic acidosis. She received continuous hemofiltration and hemodialysis, but the laboratory analyses showed no improvement. She died 11 hours after admission. Metformin is minimally bound to proteins and is readily dialyzable, but a prolonged period of dialysis is required, because metformin has a very large distribution volume and is distributed to multiple compartments. The peak blood metformin level was 432 mg/L in this case, which is one of the highest metformin concentrations ever reported, and eight hours of hemodialysis were not sufficient to reduce the serum level.

Key words: metformin, hemodialysis, lactate, acidosis

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val, 50% glucose was administered at a rate of 40 mL/h to treat hypoglycemia, which normalized her blood sugar level. Despite aggressive hemodynamic support, her serum anion gap gradually increased and the pH remained low. She died 11 hours after admission. Her respiratory status did not improve during the clinical course. Her peak serum metformin level was 432 mg/L (Fig. 2).

Discussion

The conversion of glucose to lactate in the splanchnic bed of the small intestine is promoted by metformin (2), and this leads to a shift in the intracellular redox potential from aerobic to anaerobic metabolism (3). As hepatic gluconeogenesis...
from pyruvate, alanine, and lactate is inhibited by metformin, additional lactate and substrates are available for lactate production. The most common features of metformin-associated lactic acidosis are those related to the gastrointestinal tract (e.g., nausea, vomiting, and diarrhea), followed by an altered mental status, shortness of breath, hypothermia, and hypotension (4). Therefore, when a patient who takes metformin shows abnormal vital signs, metformin-associated lactic acidosis should be considered as a differential diagnosis, especially when there is unexplained metabolic acidosis. The presence of an anion gap does not predict clinically significant hyperlactatemia, so all patients with unexplained metabolic acidosis should have their serum lactate level measured (5, 6).

By monitoring the serum metformin level during our patient’s clinical course, we found that hemodiafiltration was useful in decreasing the serum metformin level. Since metformin has a low molecular weight and its plasma protein binding is negligible, it can be removed by dialysis (up to 170 mL/min under good hemodynamic conditions) (7). CHDF was performed for eight hours, but we had trouble preventing hypotension in our case. Arroyo et al. reported a case in which continuous hemofiltration was performed because hypotension precluded the use of hemodialysis (8). Continuous hemofiltration could also be effective in lowering serum metformin level, so conducting continuous hemofiltration in our case may have improved the outcome, although the procedure was unable to save the patient.

Metformin has a mean apparent volume of distribution in the range of 63 to 276 L (7). In the present case, eight hours of hemodialysis reduced the serum metformin level from 432 to 151 mg/L, but this was not sufficient. Indeed, Seidowsky et al. showed that prolonged hemodialysis (more than 15 hours) is required to reduce the metformin levels by 90% (9).

The use of sodium bicarbonate for metformin-induced lactic acidosis has been widely debated, as it may result in an excess sodium load, rebound metabolic alkalosis, disturbances in serum potassium and calcium, a leftward shift of the hemoglobin dissociation curve, decreased myocardial contractility, increased carbon dioxide production, and reflex vasodilation after bolus injection (10).

In the setting of lactic acidosis, the associated ATP depletion may lead to vasodilatation and a further decline in systemic blood pressure. ATP normally closes ATP-dependent K⁺ channels. Thus, ATP depletion in lactic acidosis leads to the opening of these channels, resulting in K⁺ movement out of the cells. This causes hyperpolarization of the vascular smooth muscle cells, and decreased Ca²⁺ entry into these cells through voltage-dependent Ca²⁺ channels (11). The fall in the cellular Ca²⁺ concentration results in smooth muscle relaxation and a reduction in systemic vascular resistance. Because of this, the hypotension induced by metformin-associated lactic acidosis should be treated with vasoconstrictors such as noradrenaline.

The mean plasma elimination half-life of orally administered metformin is between two and six hours. Therefore, patients who ingest an excessive amount should be observed for several hours.

Metformin blood levels ranging from 0.5 to 2.0 mg/L are considered to be within the therapeutic range, whereas concentrations over 5.0 mg/L are generally considered to be toxic (13). In the present case, the peak serum metformin level was 432 mg/L. To our knowledge, this is one of the highest reported levels, with the highest level being 749 mg/L in a case reported by Sánchez-Rubio Fernandez et al. (9, 12, 13, 14).

It has recently been questioned whether metabolic acidosis with increased lactate occurs with routine metformin use. No difference between the mean serum lactate levels in patients on metformin compared with controls was noted in a large systematic review of therapeutic trials and cohort studies, although the analysis did not include any overdose cases (15). In the case of intentional overdose, a significant association was found between mortality and the logistic organ dysfunction system score, pH, serum lactate level, and prothrombin activity (9). In the present case, the low pH and high renal logistic organ dysfunction score were considered to be risk factors for mortality. However, her prothrombin activity was within the normal limits. Thus, rapid and appropriate treatment, including CHDF, should have been provided. Nevertheless, despite the correct diagnosis and treatment, the present patient died because of the extremely high levels of metformin.

Hemodialysis has been successful for treating metformin-associated lactic acidosis, but prolonged hemodialysis (more than 15 hours) is required to reduce the metformin levels sufficiently. Patients who take an overdose of metformin should therefore be carefully monitored even if dialysis is deemed unnecessary.

The authors state that they have no Conflict of Interest (COI).

References

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