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EFFECTIVE EXTRACORPOREAL TREATMENT OF METFORMIN-ASSOCIATED LACTIC ACIDOSIS USING CONTINUOUS VENOVENOUS HEMODIAFILTRATION

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ABSTRACT

Background: The prevalence of type 2 diabetes mellitus has surged globally. Metformin is recommended as the first-line oral treatment. However, metformin-associated lactic acidosis (MALA) is recognized as a rare but potentially dangerous complication. The pathogenesis of MALA is multifactorial, primarily resulting from the interference of metformin with mitochondrial function and hepatic gluconeogenesis, leading to lactate accumulation. Risk of MALA escalates with impaired kidney function, poorly controlled diabetes, fasting, and liver dysfunction.

Case Description: A 57-year-old woman with diabetes and hypertension presented with prolonged gastrointestinal symptoms. During this episode she continued using metformin. She had severe metabolic acidosis and acute kidney injury. Continuous venovenous hemodiafiltration was initiated, resulting in significant clinical improvement and normalized arterial blood gas parameters within 16 hours.

Discussion: The pharmacokinetic properties of metformin facilitate efficient elimination via hemodialysis and/or hemofiltration. Continuous venovenous hemodiafiltration emerges as effective for MALA treatment. In the case described the calculated metformin clearance during continuous venovenous hemodiafiltration was notably higher than reported values, possibly due to residual renal clearance. Clinical improvement occurred despite elevated metformin levels, suggesting a lack of correlation between metformin levels and patient outcomes. Comorbidities rather than metformin levels guide treatment decisions in MALA.

Conclusion: This case underscores the efficacy of continuous venovenous hemodiafiltration in the treatment of MALA, suggesting its potential as a standard therapeutic approach. However, further research is needed to elucidate the complex interplay between metformin levels, clinical presentation, (extracorporeal) treatment modalities and outcome in MALA.

KEYWORDS

Metformin, lactic acidosis, extracorporeal treatment, continuous venovenous hemodiafiltration

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LEARNING POINTS

- Continuous venovenous hemodiafiltration seems to be an efficient and effective treatment to eliminate metformin in patients with metformin-associated lactic acidosis.
- The metformin level does not seem to correlate with the clinical condition of the patient.
- For a comparison between the effectiveness of different renal replacement therapies in metformin-associated lactic acidosis, more research is needed.

INTRODUCTION

According to the World Health Organization the prevalence of type 2 diabetes mellitus has been increasing rapidly over the past decades in all parts of the world. Metformin, a biguanide, is recommended as first-line oral drug treatment in adults with diabetes mellitus. Therefore, metformin is a widely used drug: in 2023 approximately 682,000 individuals in The Netherlands (3.8% of the entire population) used metformin[1].

Metformin is generally well-tolerated. However, in rare instances, it can lead to a severe and potentially life-threatening complication known as metformin-associated lactic acidosis (MALA). The accumulation of metformin leads to elevated lactate levels and severe metabolic acidosis. The mechanism of these effects is multifactorial. Metformin may interfere with mitochondrial function by inhibition of the mitochondrial respiratory chain complex I, resulting in accumulation of lactate. Moreover, metformin inhibits hepatic gluconeogenesis. By inhibiting these processes metformin reduces the capacity to utilize lactate as a substrate for glucose production. These effects reduce the clearance of lactate[2]. Metformin is mainly excreted by the kidney. Therefore, MALA especially occurs in case of impaired elimination due to acute or progressive chronic kidney injury. The typical symptoms of MALA are acidotic dyspnoea, abdominal pain and hypothermia followed by a comatose state. The risk of lactic acidosis is also increased in case of poorly controlled diabetes mellitus, prolonged fasting, and/or liver dysfunction[2,3]. We present a case of an unintentional metformin intoxication that was adequately treated with continuous venovenous hemodiafiltration (CVVHDF).

CASE DESCRIPTION

A 57-year-old female, with a medical history of type 2 diabetes mellitus and hypertension, felt unwell for 4 days making it impossible for her to eat or drink properly. Despite frequent vomiting and diarrhoea, she had continued taking her medication including metformin (1000 mg twice daily) and gliclazide (80 mg twice daily) during these days. Because of these prolonged gastrointestinal complaints, she presented at the emergency department. In the ambulance she appeared to be hypoglycaemic (glucose 3.1 mmol/l) and 100 ml of glucose 50% was administered intravenously. On presentation vital signs were: blood pressure 130/70 mmHg, pulse rate 88 beats/min, respiratory rate 24 breaths/min, transcutaneous oxygen saturation 100% and temperature 35.6°C. She was somnolent and disorientated. Further physical examination was normal, apart from cold hands and feet. Initial laboratory values were significant for the following: lactate 22.9 mmol/l, creatinine 1533 µmol/l, urea 44.8 mmol/l, bicarbonate 2.8 mmol/l and potassium 8.3 mmol/l. An arterial blood gas analysis revealed pH 6.80, pCO_2 2.5 mmHg and pO_2 19.6 mmHg.

Metformin toxicity in the setting of acute kidney injury secondary to dehydration due to gastrointestinal fluid losses appeared to be the most probable explanation for her clinical condition. Fluid (Plasma Lyte 3 litres over 24 hours and 1 litre glucose 5%) and sodium bicarbonate 8.4% (400 ml) were administered and CVVHDF was started immediately after admission to the intensive care unit (ICU). The following settings were used: blood flow 150 ml/hour, pre-blood pump (PBP) citrate 1500 ml/hour, citrate dose 3.0 mmol/l, dialysis flow 400 ml/hour, substitution flow 800 ml/hour, effluent dose 30 ml/kg/hour. During the entire treatment period CVVHDF settings remained unchanged. After 16 hours CVVHDF was stopped, because there was significant clinical improvement in the patient's neurological condition and the arterial blood gas results had normalized: pH 7.40 and lactate 1,89 mmol/l. One day later the patient was discharged from the intensive care unit.

As shown in *Fig. 1* a significant decrease in metformin levels was achieved during the 16 hours of CVVHDF (from an initial concentration of 67.7 mg/l to 18.4 mg/l; therapeutic range: 0.1-4 mg/l)[4]. This reduction in metformin concentration over time suggests an elimination rate during CVVHDF (with the described settings), of approximately 3 mg/l/hour. An estimated volume of distribution of 90-450 l can be calculated based on the average volume of distribution of metformin (1-5 l/kg, based on data from the Extracorporeal Treatments in Poisoning (Extrip) Workgroup) and a weight of 90 kg[5]. Taking an average volume of distribution of 270 L into account, approximately 13 g of metformin was eliminated during 16 hours of CVVHDF. Based on an initial amount of metformin in serum of 18.3 g, approximately 71% of metformin was eliminated by CVVHDF. The calculated clearance of metformin is 356 ml/min, based on an elimination constant of 0.0792 $hour^{-1}$ during CVVHDF. This value is lower than the renal clearance of metformin in healthy adults (> 500 ml/min)[6]. Metformin levels measured in effluent show that CVVHDF contributed to the clearance and suggest that metformin is well-dialyzed since these levels

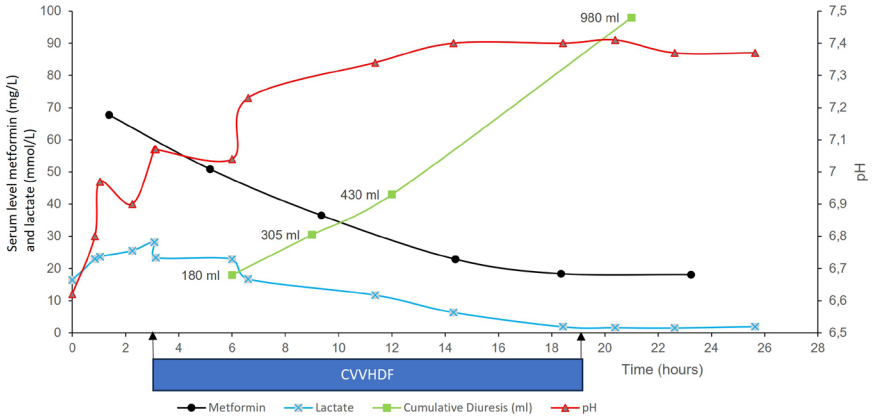

Figure 1. Metformin level, lactate level, pH and cumulative diuresis over time. The black arrows indicate the start and stop of continuous venovenous hemodiafiltration (CVVHDF).

were consistently 80-90% of the serum metformin-level. The calculated plasma elimination half-life of metformin in this case presentation is slightly prolonged compared to the average elimination half-life (range) of metformin: 8.8 hours compared to 4-8 hours.

DISCUSSION

Due to its pharmacokinetic properties metformin can be efficiently eliminated by both haemodialysis and haemofiltration. It has a low molecular weight (165 g/mol), is hydrophilic, and is not highly protein-bound and therefore possesses a low volume of distribution[6]. According to the recommendations from the Extrip Workgroup, continuous replacement therapies (CRRT) should be considered in MALA whenever lactate concentration is above 20 mmol/l and blood pH is below 7.0, as was the case in the patient described[5]. The most commonly used methods of CRRT in ICUs are continuous venovenous haemodialysis (CVVH) and CVVHDF. However, there is variation in practice worldwide. CVVHDF is a technique whereby solute and fluid removal are achieved using both diffusion and convection. Metformin does not classify as a middle molecular weight molecule since its molecular weight is significantly below the lower limit of this category. Therefore, the efficacy of removal of metformin is expected to be equal in both treatment methods. Most reports in literature describe the use of CVVH or intermittent haemodialysis (IHD) as CRRT mode used in the treatment of severe MALA[5]. A recently published case report described the use of CVVHDF in the treatment of severe metformin toxicity[6]. Based on both the findings of this case description and our findings, CVVHDF seems to be an effective treatment to eliminate metformin in patients with MALA.

In this case report, we calculated an estimated metformin-clearance of 356 ml/min. A systematic review of extracorporeal treatment in metformin poisoning, by the Extrip Workgroup, reports a median metformin-clearance of 34 ml/min in 7 cases treated with CRRT (range: 9-71.3 ml/min). A median half-life of 16.6 hours in 21 patients was found (range 9.7-45.9 hours), compared to 8.8 hours in this case report[5]. The higher clearance in our patient could be due to the combined effect of CRRT and the patient's residual renal clearance. Upon admission, the renal function of the patient was close to zero (serum creatinine 1553 µmol/l). However, during CVVHDF treatment she had an average urine output of 57 ml/hour, which could have contributed to the total clearance of metformin.

In general, a comparison between clearance values (using different renal replacement therapies) reported by other MALA case reports is rather difficult, since many varying factors (e.g., case of intoxication or therapeutic dosing, initial metformin levels, residual renal function of the patient and/or settings of renal replacement therapy) may influence these clearance values. *Figure 1* shows a flattening of the curves at approximately t=16 hours. This might indicate that CVVHDF exerts elimination with a certain threshold of metformin levels. However, the percentage of metformin in effluent solution compared to serum remained relatively constant (80-90%) during the course of dialysis.

The patient showed clinical improvement while metformin levels were still elevated. This shows that in this case, there is no correlation between metformin levels and clinical status of the patient. This lack of correlation is described by several other studies[3,5-8]. The presence of comorbidities seems to be a factor which does correlate with clinical status. In cases where MALA is suspected, the clinical presentation, lactate levels, and pH-value are leading factors regarding treatment, rather than metformin levels, since these seem to have no additional value for the treatment strategy.

CONCLUSION

This case underscores the efficacy of continuous venovenous hemodiafiltration in the treatment of MALA, suggesting its potential as a standard therapeutic approach. However, further research is needed to elucidate the complex interplay between metformin levels, clinical presentation, (extracorporeal) treatment modalities and outcome in MALA.

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