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CASE REPORT

High-volume continuous venovenous hemodiafiltration plus resin hemoperfusion improves severe metformin-associated toxicity

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ABSTRACT

We present the case of a 42-year-old female patient who attempted suicide by taking approximately 100 tablets of metformin (500 mg). Laboratory tests revealed severe lactic acidosis with lactate levels of 24 mmol/L and pH of 7.09. The patient was treated with high-volume continuous venovenous hemodiafiltration (CVVH) and resin-sorbent hemoperfusion. Metformin concentrations were measured by high-performance liquid chromatography during CVVH and hemoperfusion treatment. Before extracorporeal treatment, the plasma metformin concentration was 208.5 mg/L. After CVVH treatment for 24 h, the plasma metformin concentration had decreased to 13.9 mg/L. Resin-based sorbent hemoperfusion plus CVVH treatment had reduced the metformin plasma concentration by 61.8% after 3 h. After 7 days, the patient's laboratory tests and clinical syndrome were improved, and she was discharged from hospital. We provide evidence that CVVH plus hemoperfusion is effective in eliminating metformins and metabolic products.

INTRODUCTION

Metformin is an antidiabetic drug that became commonly available in 1959 and was approved in the USA in 1995[1]. Metformin is generally well tolerated, and has a low risk of hypoglycemia[2]. High blood lactic acid is a problem if metformin is prescribed for those with significant liver or kidney disease and in over-large doses, and metformin-associated lactic acidosis is a potentially life-threatening complication of metformin overdose[3]. There are few reports of metformin drug overdose in the literature. When metformin overdose is diagnosed, blood purification therapy is one of the essential managements. The most common extracorporeal therapy is hemodialysis and continuous venovenous hemodiafiltration (CVVH); however there is no report of the efficiency of extracorporeal metformin elimination during metformin overdose. We provide the first report of the efficiency of extracorporeal metformin elimination in a case of metformin overdose, particularly with the use of resin-based sorbent hemoperfusion. This treatment might be an important method in patients with metformin overdose causing severe lactic acidosis toxicity.

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CASE REPORT

A 42-year-old woman presented to casualty with a history of ingestion of 100 metformin tablets (500 mg each) 5 h before admission. She had developed nausea and recurrent vomiting 30 min after ingestion. On admission, she was conscious, her temperature was 36.2°C, her blood pressure was 94/50 mmHg, her heart rate was 78 b.p.m., her respiratory rate was 23 breaths/min and blood sugar was 4.89 mmol/L. Arterial blood gas showed severe metabolic acidosis and hyperlactatemia (pH 7.09 with lactate of 24.0 mmol/L). Sodium bicarbonate was administered by intravenous injection. Eight hours after admission, the patient became unconscious, and entered respiratory and cardiac arrest. She received cardiopulmonary resuscitation and full ventilatory support with endotracheal intubation. She recovered a spontaneous cardiac rhythm, with a heart rate of 85 b.p.m., breathing 15 breaths/min, blood pressure of 82/38 mmHg, blood oxygen of 100% and lactic acid concentration of 20 mmol/L. Epinephrine, atropine, dopamine and sodium bicarbonate were administered by intravenous injection. She was continued on vasopressors, and started on 50% glucose and 5% sodium bicarbonate infusions. When she developed episodes of hypoglycemia, she was injected with a glucose bolus

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by 2–4 g/h infusion to reach a target blood sugar level >3.5 mmol/L.

Because of refractory metabolic acidosis, high-volume CVVH (an effluent rate of 70 mL/kg/h) was achieved for metformin elimination at 4 h after admission. In order to determine the elimination efficiency of metformin by extracorporeal therapy, plasma metformin concentration was assayed by high-performance liquid chromatography. Before extracorporeal treatment, the patient's plasma metformin concentration was 208.5 mg/L. By 24 h after CVVH treatment, plasma metformin concentration had decreased to 13.9 mg/L. Although metformin concentration decreased after CVVH therapy, there was no significant improvement of clinical symptoms. Then, resin-based sorbent hemoperfusion and high-volume CVVH were combined as an alternative treatment. We then found a 61.8% decrease in metformin plasma concentration after treatment by 3-h resin-based sorbent hemoperfusion HA230 (Jafron Biomedical Co., Ltd, Zhuhai, China) plus CVVH. At 6 h after resin-based sorbent hemoperfusion combined with CVVH treatment, the patient's general condition was improved with blood pressure, hypoglycemia and hyperlactatemia. CVVH treatment was then continued for the next 72 h. When acid–base status returned to normal, the extracorporeal treatment was stopped. Before cessation of extracorporeal therapy, the metformin concentration was 1.2 mg/L. After extracorporeal treatment for 7 days, the patient showed normal laboratory tests and was discharged from hospital. Blood test results at presentation and treatment are shown in Table1.

DISCUSSION

Metformin is an important blood sugar-reducing drug for type 2 diabetes that has been used around the world since 1995[1]. Metformin controls blood sugar by reducing intestinal glucose uptake, inhibiting the production of hepatic glucose, and improving cell glucose absorption and utilization[4]. Metformin is absorbed primarily in the intestine, and excreted by the kidneys, but accumulates in patients with renal impairment. Accumulation of metformin can increase the risk of lactic acidosis in patients with type 2 diabetes. Metformin is consequently not recommended for patients with type 2 diabetes and glomerular filtration rate <30 mL/min/1.73 m^2[5].

Metformin is well tolerated in most patients. However, there is large variability in the hypoglycemic response to metformin. The most frequent side-effect of metformin is gastrointestinal irritation, including nausea, vomiting, diarrhea and cramps[6]. Metformin taken alone is unlikely to cause glycopenia in general patients; however, metformin overdose induces hypoglycemia and lactic acidosis[7]. Metformin-associated lactic acidosis is a serious complication, which occurs in therapeutic overdose or in patients with high-risk factors, such as renal failure and liver diseases. Patients with lactic acidosis usually show lethargy, tachypnea, tachycardia and shock. Metformin-associated lactic acidosis results in high mortality, with some patients requiring blood purification treatment.

In the case reported here, the patient with metformin overdose presented with vomiting, nausea, hypotension and severe lactic acidosis. There is no specific treatment for patients with metformin overdose. The accepted treatment of metformin overdose is support care, and includes gastrolavage, management of hypoglycemia, correction of lactic acidosis and hemodialysis[8–10]. The use of bicarbonate should be considered in well-ventilated patients with a pH <7.0. Because sodium bicarbonate infusions alone are not able to sufficiently correct the acid–base metabolism, hemodialysis or CVVH is

Table 1 | Blood results at presentation and treatment

Chemistry parameters	Before CWH	After CWH 24 h (before hemoperfusion plus CWH	After hemoperfusion plus CWH 3 h	Discharge from hospital
Urea (mmol/L)	7.9	4.4	3.8	5.4
Creatinine (μmol/L)	150	78	67	40.3
ALT	25	–	–	18
AST	33	–	–	17
Albumin	40	–	–	38.2
Bilirubin	11	–	–	10.3
Hemoglobin (g/L)	120	116	100	98
White cell ($\times 10^9$)	12.97	13.45	10.9	7.57
Platelets ($\times 10^9$)	426	354	395	384
pH	7.09	7.3	7.34	
Bicarbonate	10.4	14.8	16.7	
Base excess	−18.7	−10.5	−9.1	
Lactate (mmol/L)	24	>15	13.9	0.7
Glycemia (mmol/L)	3.66	4.5	6.8	8.4
Metformin concentration (mg/L)	208.5	13.9	5.3	1.2
HbA1c (%)	6.3	–	–	6.4

ALT, alanine transaminase; AST, aspartate transaminase; CWH, continuous venovenous hemodiafiltration; HbA1c, glycated hemoglobin.

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recommended for the clearance of metformin and to treat the acidosis. Although there are no standardized criteria for extracorporeal clearance of metformin overdose, patients with hyperlactemia (>15 mmol/L) and acidemia (pH <7.2) should be recommended for extracorporeal treatment[11].

Because metformin is a small size drug with a molecular weight of 166 Da, has a low volume of distribution and is low plasma protein binding, CVVH and hemodialysis are effective methods for elimination of metformin. Metformin is more dialyzable by intermittent hemodialysis compared with CVVH, whereas CVVH is considered superior to intermittent hemodialysis with respect to hemodynamic stability. Research in patients with end-stage renal disease shows elimination of 15% of the dose of metformin by maintenance hemodialysis. The present patient was too hemodynamically unstable to tolerate hemodialysis, and consequently CVVH was the preferred treatment.

Extracorporeal removal of metformin exceeds 200 mL/min with maintenance hemodialysis and can reach 50 mL/min with CVVH[12,13]. However, endogenous clearance is >500 mL/min in patients with normal kidney function. The method of evaluating metformin elimination is dependent on creatinine clearance and extracorporeal clearance. Therefore, residual renal function must be considered in patients with metformin overdose, because good urine output and normal renal function are very important for excretion of metformin.

Although hemodialysis or CVVH can quickly remove metformin, and decrease metformin concentration in patient plasma, the clinical symptoms of patients are not vastly improved. Because metformin is not bound to plasma proteins, hemoperfusion alone does not provide advantages compared with hemodialysis or CVVH. However, hemoperfusion plus CVVH removes more metformin and metabolic products[14]. In the present case, the patient's general condition was improved after starting resin-based sorbent hemoperfusion plus CVVH. The results suggest that the metabolic products of metformin might be one of causes of the persistent high level of lactic acid and clinical symptoms. In fact, the literature recommends hemodialysis or CVVH therapy alone, rather than hemoperfusion plus hemodialysis or hemoperfusion plus CVVH for metformin overdose. Our clinical data and metformin concentrations suggested that a combination of hemoperfusion and CVVH proved to be more effective for treatment of metformin overdose.

Measurement of concentrations in metformin overdose remains debatable, and serious toxicity can be observed in cases of chronic toxicity from metformin concentrations close to the reported therapeutic range. Because metformin concentration assays are not readily available, and no specific threshold has been confirmed as a criterion for extracorporeal clearance of metformin, more information on concentrations of metformin overdose is required[15].

There is no specific target concentration of metformin for cessation of extracorporeal therapy because of a poor correlation of concentration with outcomes. Furthermore, there are reports of cases of resistant acidemia despite negligible metformin concentrations, and even cases of a reduction of metformin concentrations with concomitant worsening of lactate levels during extracorporeal therapy. However, some experts consider that extracorporeal therapy should be continued until the concentration of metformin is <3 mg/L. Other indicators of cessation of extracorporeal therapy are a lactic acid concentration <3 mmol/L and pH of >7.35[16].

In conclusion, the present case data show that patients with metformin overdose should be treated with extracorporeal therapy. When combined with concomitant cardiovascular support and maintenance of blood glucose, extracorporeal therapy provides the possibility of a good outcome in patients with metformin overdose. A combination of CVVH and hemoperfusion eliminated more metformin and metabolic products, and improved arterial blood pressure, hypoglycemia and lactic acid in metformin overdose.

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DISCLOSURE

The authors declare no conflict of interest.

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