Metformin Associated High Anion Gap Metabolic Acidosis: A Case Report

MING-PIN WU, HOW-CHIN LIAO, SHIUMN-JEN LIAW

Metformin, a hypoglycemic agent, has been widely used to treat patients with type 2 diabetes mellitus; however, it might be related to a fatal complication: lactic acidosis. Risk factors include old age, renal function impairment, and any condition associated with tissue hypoxia, such as sepsis and myocardial infarction. Here we present a case with severe metabolic acidosis due to metformin intoxication. The 72-year-old male patient felt drowsy at home. Clinical presentations included hypoglycemia, hypotension, hypothermia, bradycardia, acute renal deterioration, and respiratory failure. Laboratory data revealed high anion gap metabolic acidosis (46.5 mEq/L) which was intractable with high doses of sodium bicarbonate. After reviewing the patient's history, we found large doses of metformin were prescribed for diabetes mellitus. Emergent hemodialysis was arranged after other possibilities were excluded and the symptoms recovered rapidly. Physicians should be familiar with clinical symptoms of metformin intoxication. Morbidity and death due to metformin intoxication include acute renal failure, electrolyte disturbance, arrhythmia and cardiovascular suppression. The role of sodium bicarbonate in the treatment is limited. Hemodialysis is the treatment of choice and should be urgently initiated.

Key words: metformin, anion gap, lactic acidosis

Introduction

Metformin (glucophage) is a well known biguanide drug which has been shown to reduce complication and mortality rates of patients with type 2 diabetes mellitus especially in the overweight patients\(^\text{(1)}\). This drug has been widely used as an oral hypoglycemic agent, but it might be related to a fatal complication: lactic acidosis. The prevalence of metformin associated metabolic acidosis is unknown but life-threatening acidosis has been estimated at 1-5 cases per 100000 patient year with a mortality rate of up to 50%\(^\text{(2)}\). In Taiwan, the incidence of metformin associated metabolic acidosis is also unknown except for some case reports. Risk factors of metformin associated metabolic acidosis include old age, renal function impairment, and any condition associated with tissue hypoxia, such as sepsis and myocardial infarction\(^\text{(2)}\), but the adverse effects could occur in patients with normal renal function (Table 1)\(^\text{(3)}\).

Here, we present a patient with diabetes mellitus treated with metformin who was admitted to our hospital with acute renal failure and severe metabolic acidosis. Despite the severity of the illness, this patient recovered completely after hemodialysis.

Case Report

A 72-year-old male patient presented with altered mental status for 4 hours. He had history
of hypertension and diabetes mellitus and had received oral anti-hypertensive and hypoglycemic agents for 20 years. He complained of headache and dizziness for about 18 hours prior to this admission. The symptoms became exaggerated and his consciousness became drowsy as time went on. Then he was brought to a local hospital for treatment where blood sugar test revealed hypoglycemia (fasting sugar, 45 mg/dL). After an injection of 2 ampules of 50% glucose water (40 g), the patient’s consciousness improved and his blood sugar rose to 150 mg/dL. Under the impression of cerebrovascular accident, the patient was referred to our hospital for further evaluation.

In our emergency department, hypotension (blood pressure, 86/32 mmHg) and hypothermia (body temperature, 32.5°C) were noted, Laboratory test results revealed leukocyte, 11390 /μL; hemoglobin, 9.7 g/dL; platelet, 327 K/μL; urea nitrogen, 74.2 mg/dL; creatinine, 6.3 mg/dL; albumin, 4.1 g/dL; cholesterol, 173 mg/dL; triglycerol, 172 mg/dL; uric acid, 15.5 mg/dL; sodium, 130 mEq/L; potassium, 6.1 mEq/L; chloride, 82 mEq/L; calcium, 8.5 mg/dL; magnesium, 1.6 mg/dL; troponin I, 0.07 ng/ml; and osmolality, 318 mosm/L; His arterial blood gas (ABG) results included: pH, 6.788; PaCO₂, 10.0 mmHg; PaO₂, 142.4 mmHg; HCO₃⁻, 1.5 mmol/L; and base excess (BE), –29 mmol/L. His anion gap was calculated at about 46.5 mEq/L, APACHE II score on admission was 29.

Due to severe metabolic acidosis, the patient was admitted to our intensive care unit after 6 ampules of sodium bicarbonate (102 mEq) injection. During admission, rapid deterioration of consciousness, atrial fibrillation with slow ventricular rate and hypotension (systolic blood pressure around 40-50 mmHg) were noted. The patient was intubated due to his rapidly deteriorating condition. Although aggressive fluid challenge and vasoactive agent was used (dopamine), the patient’s blood pressure was still low (systolic blood pressure around 80-90 mmHg). Intractable metabolic acidosis (ABG: pH, 6.967; PaCO₂, 15.1 mmHg; PaO₂, 561.5 mmHg; HCO₃⁻, 3.4 mmol/L; and BE, –26 mmol/L) persisted although large amounts of sodium bicarbonate were used (24 ampules, 408 mEq).

Emergent hemodialysis was arranged 4 hours later after admission for intractable metabolic acidosis. Then his relatives brought us the prescribed medications from home: Norvasc 1# qd for hypertension and Glucophage 2# tid for diabetes mellitus. According to the statement of the family and the medical records from the local hospital, chronic renal insufficiency was noted (creatinine, 2.3 mg/dL) and metformin 1000 mg three times daily had been prescribed for several years. Metformin induced high anion gap metabolic acidosis was highly suggested. During hemodialysis, the patient’s consciousness improved rapidly and blood pressure returned to normal range. After dialysis, the patient’s consciousness was alert and serum lactate level was 5.7 mEq/L.

Polyuria was noted after repeated hemodialysis
on the second day and his creatinine level dropped to 2.4 mg/dL. Metabolic acidosis improved gradually without sodium bicarbonate needed. Endotracheal tube was removed on day 3.

There was no neurological sequel left. On the day of his discharge after 12 days of hospitalization, oral hypoglycemia agents were shifted to glimepiride (amaryl) and acarbose (glucobay).

**Discussion**

High anion gap metabolic acidosis might be due to several causes, such as diabetic ketoacidosis, methanol intoxication, salicylic acid ingestion, renal failure, sepsis and lactic acidosis. Our patient did not have history of alcohol abuse or intake of salicylate. Diabetic ketoacidosis was excluded due to the negative results for blood and urine ketone bodies. Renal function deterioration could be related to metabolic acidosis but the pH and bicarbonate of ABG seldom drop to such low level. Sepsis could be confused due to the similarity of symptoms. There was no chills or fever; leukocytes were not elevated and cultures for infection all reveal negative results. We did not use antibiotics throughout the admission period. Sepsis associated metabolic acidosis was not likely.

Lactic acidosis is the most severe side effect of taking metformin. The exact mechanism by which metformin is associated with lactic acidosis is uncertain\(^4\). It has been traditionally thought to be the result of the shift toward anaerobic intracellular metabolism, which yields large quantities of lactate, coupled with impaired utilization due to suppression of hepatic gluconeogenesis\(^5\). Most cases that have been reported occurred in type 2 diabetic patients with renal failure\(^6\). Clinical presentations include gastrointestinal dysfunction, change in consciousness, hypothermia, hypotension, and bradycardia (Table 2). Laboratory findings in patients with metformin associated metabolic acidosis usually include elevated blood lactic acid concentrations (>5 mEq/L), decreased blood pH (<7.25), and increased anion gap (>15 mEq/L)\(^5\). When metformin is responsible for metabolic acidosis, plasma metformin concentrations are usually above 5μg/mL\(^7\). Our patient satisfied above criteria except for the metformin concentration which was unavailable.

Metformin associated morbidity and mortality rates are due to acute renal failure, electrolyte disturbance, arrhythmia and cardiovascular suppression\(^8\). Severe cardiovascular collapse due to acidosis occurred despite large amounts of sodium bicarbonate infusion. Correction of acidosis using sodium bicarbonate alone is ineffective in most cases due to continuous lactate production resulting from prolonged action of the metformin\(^9\).

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Therefore, the role of sodium bicarbonate in the treatment of metformin associated metabolic acidosis is limited.

The excellent outcome of our patient might be from early initiation of effective treatment. Hemodialysis can reverse ongoing metabolic acidosis and is the treatment of choice in metformin associated metabolic acidosis\(^{10,11}\). It does not only correct acidosis but also removes metformin and lactate from plasma\(^{11}\). Failure to recognize the cause of acidosis might lead to delays in hemodialysis. In our case, high doses of metformin were prescribed although the patient had impaired renal function. The potential risk factor triggering the onset of metformin associated acidosis might have been acute renal deteriorarion. Before medication records were available, the cause of severe metabolic acidosis was obscured. We tried to correct acidosis using sodium bicarbonate but in vain. Emergent hemodialysis was arranged for renal failure and unresponsive metabolic acidosis. Although lactic acid levels before hemodialysis were missed, post hemodialysis lactic acid levels remained high.

Hypothermia has occasionally been observed in metformin associated metabolic acidosis. Warming might result in a critically systemic inflammatory response syndrome\(^{8,12}\). In our patient, the initial body temperature was 32.5\(^\circ\)C which returned to normal range gradually after hemodialysis without active rewarming.

One researcher reported on 10 patients treated with metformin who were found to suffer from severe metabolic acidosis\(^{13}\). The age range was 55-83 years (average, 68.5 years) and the baseline creatinine on admission ranged from 5.0 to 16.1 mg/dL (average, 9.54 mg/dL). Plasma metformin concentrations were not measured, but each patient was either on 850 mg twice daily or 1000 mg twice daily. All were extremely ill (APACHE mean score, 30.8; range, 21-44). Apart from one patient who died 48 hours after admission, the others improved substantially within 24 hours. Despite the severity of their illnesses, patients had excellent survival rates and rapid reversal of acidosis. In our case, the patient developed acute renal failure and profound metabolic acidosis. The clinical situation was similar to each other.

In one paper published from Taiwan in 2002, researchers described two patients who suffered from metabolic acidosis caused by metformin which resulted in a suicide attempt\(^9\). Laboratory data also showed metabolic acidosis with high anion gap. One patient recovered completely and the other died of multiple organ failure. The authors concluded that metformin intoxication should be suggested when patients present with high anion gap metabolic acidosis and hemodialysis should be initiated as soon as possible in addition to other supportive care. We stabilized our patient’s hemodynamic status with aggressive hydration plus vasoactive agent and started hemodialysis 4 hours after admission. The treatment was effective and no obvious sequel was left.

In conclusion, metformin associated metabolic acidosis is a rare but critical condition in type 2 diabetic patients. Clinical symptoms of intoxication should be known by physicians. Small numbers of patients under regular metformin treatment present with lactic acidosis. The risk of metformin associated metabolic acidosis predominantly relates to old age, renal insufficiency and any diseases causing tissue hypoxia. Hemodialysis is the treatment of choice and should be initiated urgently.

References

Metformin引起之高陰離子間隙代謝性酸中毒

吳銘斌 廖浩欽 廖訓禎

Metformin是一種口服的降血糖藥，目前已被廣泛使用在治療第二型糖尿病病患。雖然少見，該藥卻潛藏著致命的併發症：乳酸性酸中毒。可能致病的危險因子包括：高齡、腎功能不全、以及任何可能導致組織缺氧之因素，如敗血症、心肌梗塞等。在此我們報告一位72歲男性因為服用Metformin造成嚴重的代謝性酸中毒。病患因意識不清入院，臨床表現有低血糖、低血壓、低體溫、心博過緩、急性腎衰竭及呼吸衰竭。檢驗數值呈現高陰離子間隙之代謝性酸中毒（46.5 Meq/L），無法以高劑量重碳酸鹽矯正。回顧用藥史發現，病人腎功能不佳卻仍使用大劑量Metformin治療糖尿病。經安排緊急洗腎後病人的症狀迅速緩解。臨床醫師應對Metformin引起代謝性酸中毒之臨床症狀有所警覺。死亡原因包括急性腎衰竭、電解質不平衡、心律不整及心血管功能衰竭。重碳酸鹽無法改善其代謝性酸中毒，治療的選擇為安排血液透析。若能儘早治療，病患的預後通常很好。

關鍵詞：Metformin，陰離子間隙，乳酸性酸中毒