METFORMIN-ASSOCIATED LACTIC ACIDOSIS FOLLOWING CONTRAST-INDUCED NEPHROPATHY

Yu-Feng Liang¹, Yen-Kuang Tai²

Abstract

Metformin has been recommended as the first-line therapeutic option for diabetes mellitus. Lactic acidosis is a rare but life-threatening side effect of metformin. In previously reported cases, the occurrence of metformin-associated lactic acidosis (MALA) was usually accompanied by acute kidney injury (AKI). Among these risk factors for AKI, concurrent use of nephrotoxic agent, such as contrast medium, is common but often ignored in clinical practice. We present an elderly diabetic patient who was initially hospitalized due to complete AV block associated with AKI. After supportive therapy and temporary pacemaker implantation, the renal function recovered 5 days later. Metformin was prescribed again for better glucose control; CT angiography of bilateral lower limbs was then performed to prepare for revascularization. Four days later, acute renal failure with high anion gap metabolic acidosis manifesting as bradycardia with conscious change was noted. After exclusion of other etiologies, the diagnosis of MALA following contrast medium-induced nephropathy (CIN) was made. In view of hypotension and increased respiratory distress, vasopressors and ventilator support were instituted immediately. To correct acidosis and remove lactate as well as metformin, emergent hemodialysis was also initiated within 2 hours. However, despite intensive support of cardiovascular, respiratory and renal system, the patient died of sepsis with multiple organ failure 6 days later. We present this case to remind clinicians that metformin should be discontinued in diabetic patients receiving intravascular contrast study. For hospitalized patients, metformin should only be reused if reassessed renal function 48 hours after contrast medium administration has not deteriorated.

Key Words: Metformin, Contrast-induced nephropathy, Lactic acidosis, Acute kidney injury

Introduction

Since the benefits on diabetic and cardiovascular complications were established in the UK Prospective Diabetes Study, metformin has been increasingly used for management of hyperglycemia.¹ In fact, it is nowadays the first-line therapeutic option for type 2 diabetes.² However, lactic
acidosis, a rare but life-threatening side effect of metformin, is persistently a great concern by clinicians. In previously reported cases, metformin-associated lactic acidosis (MALA) was usually accompanied by acute kidney injury (AKI). Hence, some risk factors, such as preexisting renal dysfunction, old age and nephrotoxic agents have been suggested either as contraindications or to be used with caution. Among the various nephrotoxic agents, iodinated contrast medium is a commonly used, but often ignored one in a modern well-facilitated hospital. Not a few clinicians do not realize that metformin and contrast medium might be a dangerous combination under certain situations. Here we present an elderly diabetic patient who received metformin and intravascular contrast study concurrently, leading to a fatal outcome.

**Case Report**

This 89-year-old man presented to our emergency department with sudden onset of dizziness and general weakness for one hour. His conscious level was clear, blood pressure was 145/65 mmHg, pulse rate was 46 beats/min, and body temperature was 36.4°C. On physical examination, dry gangrenous change over right 3rd to 5th toes were noted. Past medical illness included diabetes mellitus and hypertension for more than 20 years. His diabetes was controlled by gliclazide 160 mg and metformin 1000 mg twice daily. Laboratory results showed BUN 45 mg/dL, Cr 1.9 mg/dL, GOT 23 U/L, GPT 19 U/L, Glucose 396 mg/dL, HbA1c 7.1%, WBC 16.9 x 10^3 /uL, CRP 19.9 mg/L, Na 122 meq/L, K 5.2 meq/L, arterial blood gas analysis revealed pH 7.374, PCO\(_2\) 27.5 mmHg, PO\(_2\) 102 mmHg, HCO\(_3^-\) 16.2 mmol/L and BE -6.8 mmol/L. Since EKG showed complete AV block, temporary pacemaker was implanted and the patient was admitted to the intensive care unit. After admission, insulin therapy was used instead of oral antidiabetic agents. With supportive therapy, renal function turned to be normal (BUN/Cr: 18/1.0 mg/dL) as well as complete cell counts and electrolytes 5 days later. The temporary pacemaker was removed on 6th hospital day. Cardiac sonogram revealed normal wall motion with ejection fraction of 75.2%. Under the suggestion by cardiovascular surgeon, CT angiography of bilateral lower limbs was arranged to prepare for revascularization. At the same time, metformin was prescribed again with dosage of 1000 mg twice daily for better glucose control. Unfortunately, on 4th day after performing CT angiography, acute onset of bradycardia (40 beats/min) with blood pressure of 116/51 mmHg and disturbed consciousness were noted. The arterial blood gas analysis showed PH 6.802, PCO\(_2\) 39.3 mmHg, PO\(_2\) 102 mmHg, HCO\(_3^-\) 6.2 mmol/L and BE -26.2 mmol/L. High anion gap (39.8 meq/L) metabolic acidosis was documented. In addition, urgent laboratory results revealed BUN 86 mg/dL, Cr 6.8 mg/dL, Na 135 meq/L, K 6.0 meq/L, Ca 8.8 mg/dL, P 11.2 mg/dL, WBC 12.4 x 10^3 /uL, CRP 32 mg/L and lactic acid 26.6 mmol/L. Blood glucose was 131 mg/dL and blood ketone body was negative. Although a large amount of intravenous sodium bicarbonate (340 mmol) was infused, clinical condition deteriorated rapidly and blood pressure dropped to around 90-100/45-55 mmHg accompanied by intractable metabolic acidosis (PH 7.00~7.05) within one hour. Therefore, vasoactive agents were used and ventilator therapy was started. Furthermore, because of acute renal failure and highly suspected metformin-associated lactic acidosis, emergent hemodialysis was also initiated immediately. In the intensive care unit, the patient received hemodialysis (4 hours/session) for consecutive three days. General condition improved initially. However, despite intensive support of cardiovascular, respiratory, and renal system, the patient died of sepsis with multiple organ failure six days later (17th hospital day).

**Discussion**

Our patient had near-normal renal function just before CT angiography, but acute renal failure was noted 4 days later. In the absence of other significant risk factors for AKI, contrast-induced nephropathy (CIN) seemed to be the most likely
cause. Iodine-based contrast media accounts for 10% of all causes of hospital-acquired acute renal failure and represents the third leading cause of in-hospital renal function deterioration. CIN is defined as an impairment of renal function that occurs within 72 hours of administering contrast medium. The renal dysfunction is characterized by an increase in serum creatinine of at least 0.5 mg/dL or 25% above baseline. Serum creatinine typically peaks three to five days after contrast administration. The risk factors for CIN are shown in Table 1. Pre-existing renal dysfunction in diabetic patients is the most important risk factor, and the associated incidence of CIN is 12-27%, compared with an incidence of 0-5% in patients with normal renal function. Our patient just suffered from AKI one week prior to this contrast procedure. Although renal function partially recovered after treatment, our patient should be considered to have unstable renal function. The contrast medium our patient received is iohexol, a non-ionic and low osmolar agent. Using the CIN risk score developed by Mehran et al., our patient was estimated to have a risk of renal damage of greater than 25% and greater than 1% risk of requiring dialysis. However, the situation was further complicated by subsequent development of lactic acidosis.

The pathogenesis of contrast-induced renal failure is complex and not well understood. It appears to be a result of direct contrast-induced renal tubular injury and renal vasoconstriction-induced medullary hypoxia. The key mechanism seems to be alteration in renal dynamics, probably caused by imbalances between vasodilator and vasoconstrictor factors, including the activities of nitric oxide, prostaglandins, endothelin, and reactive oxygen species.

Volume expansion with either normal saline or sodium bicarbonate has been recommended as the preventive strategy for CIN. At the present time, no pharmacological prophylaxis has yet been shown to offer consistent protection against CIN.

The in-hospital mortality rate in patients developing renal insufficiency is directly related to the increment of serum creatinine concentration. The mortality rate ranges from 3.8% with an increase in serum creatinine level of 0.5 to 0.9 mg/dL to 64% with an increase of greater than 3.0 mg/dL. Deaths from renal failure (metabolic acidosis, hyperkalemia and fluid overload) are rare;

Table 1. Risk factors for contrast medium-induced nephropathy

<table>
<thead>
<tr>
<th>Source</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related</td>
<td>Renal insufficiency&lt;br&gt;eGFR &lt; 60ml/min for intra-arterial administration&lt;br&gt;eGFR &lt; 45ml/min for intra-venous administration&lt;br&gt;Diabetes mellitus&lt;br&gt;Dehydration&lt;br&gt;Poor cardiac function (e.g. Congestive heart failure NYHA grade 3-4, low LVEF, Recent myocardial infarction)&lt;br&gt;Hypotension&lt;br&gt;Age over 70&lt;br&gt;Anemia&lt;br&gt;Concurrent administration of nephrotoxic drugs</td>
</tr>
<tr>
<td>Procedure-related</td>
<td>Intra-arterial administration&lt;br&gt;High osmolality agents&lt;br&gt;Large doses&lt;br&gt;Multiple doses within 72 hours</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction
most contrast-induced nephropathy patients die of sepsis, bleeding, or respiratory failure.\textsuperscript{12}

The occurrence of high anion gap metabolic acidosis following acute renal failure in our patient alerted the clinician to the diagnosis of lactic acidosis. Ketoacidosis and offending medications, such as salicylates, ethylene glycol and methanol, were excluded by laboratory results and medication record. Renal failure could produce metabolic acidosis but seldom result in such a low pH value. In addition, the patient had no preexisting liver disease, cardiac failure and hypoxic conditions associated with increased lactate level. Hence, the diagnosis of MALA was made after documentation of metabolic acidosis (pH < 7.35, HCO$_3^-$ < 22 mmol/L) and elevated plasma lactate > 5 mmol/L in this patient taking metformin.\textsuperscript{15}

The mechanism of lactic acidosis induced by metformin is thought to be mainly a combined effect of increased lactate production by a shift in intracellular redox potential from aerobic to anaerobic metabolism and decreased lactate utilization by suppressed hepatic glucose production.\textsuperscript{14} The correlation between metformin use and lactic acidosis is a debatable issue. Salpeter et al. in a meta-analysis of 347 comparative trials and cohort studies concluded that metformin is not associated with an increased risk of lactic acidosis.\textsuperscript{15} Nevertheless, in real-life practice, MALA, usually accompanied by acute kidney injury, was continuously reported worldwide.\textsuperscript{5,13,14} Metformin is mainly excreted unchanged by the kidney with 90% excreted in the first 12 hour.\textsuperscript{16} In moderate or severe renal impairment, metformin excretion is reduced by more than 70%\textsuperscript{17} and blood metformin concentration may be many times greater than the therapeutic level, potentially increasing the risk of lactic acidosis.\textsuperscript{17} In some reported cases, the occurrence of MALA solely after taking large dose of metformin further highlighted the role of drug accumulation in the pathogenesis.\textsuperscript{13,19} Obviously, because of contrast medium-induced acute renal failure, metformin of near-maximal dose accumulated rapidly in our patient and potentiated the development of lactic acidosis.

Metformin is not a risk factor for developing CIN. However, just like our patient, serious complications (lactic acidosis) may occur rarely in patients taking metformin who subsequently develop acute renal failure. Therefore, for patient safety, metformin often needs to be discontinued in diabetics undergoing iodine-based contrast studies. Whether this should be done at the time of contrast injection or 48 hours prior to it remains somewhat controversial, as does the question of whether metformin must be discontinued for all patients or only for those with renal impairment. As the safety of metformin became clearer, a relaxation of the guidelines for metformin was proposed.\textsuperscript{20} Nevertheless, partly due to the low evidence level, substantial inconsistencies exist between the recommendations of the current international guidelines about contrast medium administration in patients taking metformin.\textsuperscript{7} The new European Society of Urogenital Radiology guideline states that patients with an eGFR of 45 ml/min/1.73 m$^2$ or greater can continue to take metformin normally if they receive intravenous iodinated contrast medium. Patients with an eGFR of 30-44 ml/min/1.73 m$^2$ should stop taking metformin 48h before contrast medium administration. Reassessment of renal function 48h after contrast medium is recommended and metformin should only be restarted if the renal function has not deteriorated further.\textsuperscript{18} By contrast, both Canadian Association of Radiologists\textsuperscript{20} and American College of Radiology\textsuperscript{21} recommend clinicians to stop metformin just at time of injection in patients with renal impairment. As shown in Table 2, the Diabetes Association of the Republic of China

<table>
<thead>
<tr>
<th><strong>Table 2. Contraindications to the use of metformin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conditions associated with tissue hypoxia</strong></td>
</tr>
<tr>
<td>Hepatic and cardiac failure</td>
</tr>
<tr>
<td>Age over 80</td>
</tr>
<tr>
<td>Renal impairment</td>
</tr>
<tr>
<td>Serum creatinine $\geq$ 1.5 mg/dL for men;</td>
</tr>
<tr>
<td>Serum creatinine $\geq$ 1.4 mg/dL for women or</td>
</tr>
<tr>
<td>eGFR $&lt; 30$ ml/min/1.73 m$^2$</td>
</tr>
<tr>
<td>Intravenous contrast medium administration</td>
</tr>
</tbody>
</table>

\textsuperscript{eGFR, estimated glomerular filtration rate}
even recommends that metformin should not be used for diabetic patients receiving intravascular contrast medium.\textsuperscript{22} However, in our case, if the clinician was aware of the high risk for CIN and did not reuse metformin or could reassess renal function more closely, that’s 48 hours after the contrast procedure, the fatal outcome might be preventable.

The prognosis of MALA depends on the underlying disease. It has been reported with a mortality rate of 30-50%.\textsuperscript{23-24} Neither metformin concentrations nor lactate levels seem to predict outcome in MALA.\textsuperscript{25,26} Recent studies pointed out liver disease as more important risk and prognostic factors.\textsuperscript{5,23} Peters et al. found that shock on admission to ICU and prothrombin time were related to a higher mortality.\textsuperscript{23} The incidence and prognosis of MALA specifically related to concurrent use of contrast medium was rarely investigated. A review of published cases of metformin-induced lactic acidosis showed that 8% occurred in presence of contrast induced nephropathy.\textsuperscript{27} McCartney MM et al. found fatal outcome in 8 out of 18 cases with MALA after the use of contrast medium.\textsuperscript{28}

In conclusion, concurrent use of metformin and contrast medium might be dangerous for diabetic patients; the occurrence of CIN would lead to accumulation of metformin and development of lactic acidosis with high mortality. All clinicians should be aware of the risk factors for CIN. Prophylactic measures including adequate hydration and maintenance of hemodynamic stability along with the avoidance of nephrotoxic medications help to preserve renal function. To prevent lactic acidosis, we recommend clinicians to discontinue metformin before or at time of contrast medium administration. Metformin should only be reused if retested renal function 48 hours after contrast medium administration has not deteriorated.

References


17. Sambol NC, Chiang J, Lin ET, et al. Kidney function and age are both predictors of pharmacokinetics of
Metformin and contrast medium in diabetes

119

顯影劑腎病變導致 metformin 相關的乳酸中毒

梁宇峰¹，戴研光²

摘要

Metformin 目前是治療糖尿病的首選藥物，乳酸中毒則是與 Metformin 治療相關的一種罕見卻可能致命的副作用。過去的個案報告裡，Metformin 相關的乳酸中毒常伴隨著急性腎損傷，而在這些可能的危險因子當中，同時使用腎毒性藥物，譬如含碘顯影劑，在臨床上則是常見卻容易被忽略的。我們報告一位年老的糖尿病患最初是因為完全性的房室阻斷合併急性腎損傷而住院，經支持療法及置放暫時性心臟節律器後，腎功能於五天後恢復正常，Metformin 再度被使用以改善血糖控制，同時，由於腳趾呈壞疽現象，因此安排雙下肢的電腦斷層血管攝影檢查。然而，四天之後，突發心律過慢且意識障礙，血液檢查發現急性腎衰竭合併高陰離子間隙代謝性酸中毒，經排除其他可能的致病因子，依據病史、臨床特徵及檢驗數據診斷，可能是顯影劑引發急性腎衰竭之後，導致 Metformin 的堆積而引起乳酸中毒。由於低血壓及呼吸衰竭，立刻使用升壓劑及呼吸器治療，且為了矯治嚴重的酸中性毒以及排除乳酸及 Metformin，緊急施以血液透析術。雖然在心血管、呼吸及腎臟方面的積極治療，病患仍於六天後死於敗血症。本案例提醒臨床醫師，當糖尿病患欲接受含碘顯影劑檢查時，應停止使用 Metformin。對於住院病患，唯有當造影檢查結束 48 小時後重測的腎功能指數顯示並未惡化，才能再度使用 Metformin。

關鍵詞：metformin，顯影劑腎病變，乳酸中毒，急性腎損傷

聯絡人：戴研光醫師
802 高雄市長成功一路 162 號：阮綜合醫療社團法人阮綜合醫院新陳代謝科
電話：07-335-1121 轉 2310；傳真：07-335-4114；E-mail：yk.tai@msa.hinet.net
阮綜合醫療社團法人阮綜合醫院內科部 胸腔暨重症醫學科