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# The importance of early haemodiafiltration in the treatment of lactic acidosis associated with the administration of metformin

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Nefrologia 2012;32(5):664-9
doi:10.3265/Nefrologia.pre2012.Jun.11395

## ABSTRACT

Metformin is a drug widely used in type 2 diabetic patients. The metformin-associated lactic acidosis (MALA) in diabetic patients is rare but can be serious. However, the relationship between metformin and lactic acidosis has been controversial. We present seven cases of patients with MALA who came to our centre over a period of one year and who were treated early with hemofiltration. There are some risk factors that appear to predispose to the pathology, such as: acute renal failure, hypoxemia, and sepsis situations, cardiac or respiratory failure, previous history of lactic acidosis, liver disease, and dehydration boxes. That is why their use is discouraged in patients with GFR below 30mL/min/1.73m$^2$. All patients described were treated early with hemofiltration. The mortality in our series was 16.6%. We believe that the MALA is a serious condition that requires prompt diagnosis and early treatment. Renal replacement therapy is not the solution for all patients but can improve prognosis in those more severe if started early. We should limit the use of metformin in diabetic patients with impaired renal function, although there is still controversy in the various published studies.

**Keywords:** Metformin. Lactic acidosis. Kidney failure. Hemodiafiltration.

## *Importancia de la hemodiafiltración precoz en el tratamiento de la acidosis láctica asociada a la administración de metformina*

### *RESUMEN*

*La metformina es un fármaco muy utilizado en pacientes con diabetes tipo 2. La acidosis láctica asociada a metformina (ALAM) en pacientes diabéticos es poco frecuente, pero puede llegar a ser grave. De todas formas, la relación entre metformina y acidosis láctica ha sido muy controvertida. Presentamos siete casos de pacientes con ALAM que llegaron a nuestro centro en un período de un año y que fueron tratados de forma precoz con hemofiltración. Existen algunos factores de riesgo que parecen predisponer a esa patología, como fracaso renal agudo, situaciones de hipoxemia y sepsis, insuficiencia cardíaca o respiratoria, historia previa de acidosis láctica, hepatopatía y en cuadros de deshidratación. Es por ello por lo que se desaconseja su utilización en pacientes con filtrado glomerular inferior a 30 ml/min/1,73 m$^2$. Todos los pacientes que presentamos fueron tratados de forma precoz con hemofiltración. La mortalidad de nuestra serie fue del 16,6%. Consideramos que la ALAM es una enfermedad grave que requiere un diagnóstico y un tratamiento precoces. El tratamiento renal sustitutivo no es la solución para todos los pacientes, pero puede mejorar el pronóstico en aquellos que están más graves si se inicia de forma precoz. Creemos importante limitar el uso de la metformina en los pacientes diabéticos con función renal alterada, a pesar de que todavía existe controversia en los distintos estudios publicados.*

***Palabras clave:*** *Metformina. Acidosis láctica. Insuficiencia renal. Hemodiafiltración.*

## INTRODUCTION

Metformin is a drug frequently used in type 2 diabetes patients. Metformin-associated lactic acidosis (MALA) is an uncommon complication with high mortality rates in

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diabetic patients. The relationship between metformin and lactic acidosis is currently a subject of debate; despite the recent Cochrane review in which no contraindications were provided against administering metformin, several authors have provided evidence for a relationship between this drug and the development of this important complication.

The objective of our study was to determine the diagnosis, early treatment and survival of a series of MALA patients. We examined 7 cases of MALA that arrived at our hospital during a 1-year period and that were treated early with haemodiafiltration.

## CLINICAL OBSERVATIONS

### Case 1

A 63-year old male with type 2 diabetes on treatment with metformin at 850mg/8h, hypertension, hyperuricemia, obstructive sleep apnoea-hypopnoea syndrome, normochromic normocytic anaemia and stage 3A chronic renal failure (estimated glomerular filtration rate [eGFR]: 35ml/min/1.73m$^2$ –MDRD-). The patient sought treatment at his reference hospital due to anuria with 24 hours evolution along with hypogastralgia, diarrhoea and dyspnoea, but no fever or haemodynamic instability. The initial laboratory analysis is described in the Table 1, with the notable result of worsening renal function and hyperkalaemia, with severe metabolic acidosis and elevated lactate and anion GAP levels. The patient also suffered from psychomotor agitation, tachypnoea, a tendency toward arterial hypotension and hypoventilation, for which he was intubated and administered dopamine perfusion. Sodium bicarbonate was also administered to correct the pH imbalance and treatment was started for the hyperkalaemia. The patient was then transferred to our centre, where he was admitted to the intensive care unit (ICU). Upon arrival, the patient's metabolic acidosis and hyperkalaemia were being corrected, but we observed a substantial increase in blood lactate levels and haemodynamic instability. The patient continued to suffer anuria. We started the patient on continuous veno-venous haemodiafiltration (CVHDF), bicarbonate, a perfusion of noradrenaline and dopamine, as well as empirical antibiotic treatment with piperacillin-tazobactam, although no parameters of sepsis were observed and cell cultures were negative. The patient was extubated 5 days after arrival in the ICU. Amine perfusion was removed 72 hours after hospitalisation. The CVHDF treatment was maintained for 5 days, until spontaneous diuresis commenced. The patient was then transferred to nephrology with no requirements for haemodialysis. The patient was discharged after 16 days in the hospital, with an eGFR of 32ml/min/1.73m$^2$, which was sustained throughout the outpatient follow-up period.

### Case 2

A 75-year old male with type 2 diabetes on treatment with metformin at 850mg/8h, hypertension, chronic obstructive pulmonary disease (COPD), and stage 3A chronic renal failure (eGFR: 35ml/min/1.73m$^2$ –MDRD-), who sought treatment at another hospital for symptoms including diarrhoea, dyspnoea, and oligoanuria of 8 days evolution. Upon arrival at the centre, the patient was haemodynamically stable. The initial laboratory analysis results are described in the Table 1; notable findings included severe metabolic acidosis with an elevated anion GAP, worsening renal function and severe hyperkalaemia. Electrocardiogram tests revealed sinus tachycardia with peaked T-waves. Neither the metabolic acidosis nor hyperkalaemia were treated and the patient was transferred to our hospital. Upon arrival, the patient had a blood pressure (BP) of 95/50, with worsening metabolic acidosis and increased lactate levels. The patient was admitted to the ICU, where CVHDF was commenced along with noradrenaline perfusion, which was then removed after 24 hours. The state of acidosis was treated with sodium bicarbonate, along with empirical antibiotic treatment with ceftriaxone, with no increase in parameters of sepsis and negative culture results. The patient was also started on non-invasive mechanical ventilation with no need for intubation. CVHDF was maintained for 2 days until spontaneous diuresis commenced along with improved renal function, with no need for later haemodialysis sessions. The patient was discharged with an eGFR>60ml/min/1.73m$^2$, under outpatient follow-up control.

### Case 3

A 70-year old male with type 2 diabetes on treatment with gliclazide and metformin at 850mg/8h, with hypertension and benign prostatic hyperplasia, sought treatment at another hospital due to general discomfort and vomiting with 48 hours evolution. Renal function prior to this point was normal. Upon arrival, the patient was haemodynamically stable. Initial laboratory values are summarised in the Table 1. Notable results included severe metabolic acidosis with an elevated anion GAP, worsening renal function and severe hyperkalaemia. Treatment was started for the hyperkalaemia and metabolic acidosis, and the patient was transferred to our hospital. Upon arrival, we observed worsening renal function, with increased blood lactate levels. An electrocardiogram revealed sinus rhythm with peaked T-waves. Given the patient's stable condition, we administered sodium bicarbonate and conventional intermittent haemodiafiltration, which was tolerated without incident. The patient progressed favourably, with normalised laboratory values and no need for new sessions of haemodialysis. The patient was discharged 5 days after hospitalisation, with an eGFR>60ml/min/1.73m$^2$, under outpatient follow-up control.

**Table 1.** Patient characteristics

| | CASE 1 | CASE 2 | CASE 3 | CASE 4 | CASE 5 | CASE 6 | CASE 7 |
|---|---|---|---|---|---|---|---|
| **Sex/age** | Male/63 years | Male/75 years | Male/70 years | Female/78 years | Male/76 years | Male/52 years | Male/75 years |
| **Background** | Type 2 DM (Metformin), AHT, OSAHS, CRF (GFR: 35-40) | Type 2 DM (metformin), AHT, COPD, CRF (GFR: 35) | Type 2 DM (metformin + gliclazide), AHT, BPH | Type 2 DM (metformin), AHT | Type 2 DM (metformin, vildagliptin), COPD, nephrolithiasis | Type 2 DM (metformin), COPD | Type 2 DM (metformin), AHT, asthma |
| **Reason for seeking treatment** | - Hypogastralgia,<br>- Diarrhoea,<br>- Dyspnoea,<br>- Anuria (24h) | - Hypogastralgia,<br>- Diarrhoea,<br>- Dyspnoea,<br>- Oligoanuria | - General discomfort,<br>- Vomiting | - General discomfort,<br>- Interscapular pain,<br>- Diarrhoea | - General discomfort,<br>- Abdominal pain | - General discomfort,<br>- Diarrhoea,<br>- Reduced consciousness (GCS: 10) | - General discomfort,<br>- Fever,<br>- Abdominal pain,<br>- Vomiting |
| **Initial BP** | 140/72 | 138/46 | 131/51 | 132/52 | 200/110 | 170/120 | 136/86 |
| **Creatinine** | 10 | 14 | 10.4 | 1.7 | 11 | 13.7 | 1.5 |
| **Urea** | 135 | 320 | 200 | 121 | 251 | 219 | 44 |
| **Na/K (mEq/L)** | 136/7.8 | 135/8 | 135/9 | 128/5.7 | /6.7 | /5.6 | 141/3.5 |
| **pH** | 6.8 | 7.11 | 6.9 | 6.9 | 6.96 | 6.8 | 7.32 |
| **Bicarbonate** | 13 | 9.2 | 7.6 | 11.1 | 4 | - | 21 |
| **Lactate** | 14 | - | - | - | - | - | - |
| **Anion GAP** | 23 | 49 | 30 | 21 | - | | - |
| **Time to transferral** | 5 hours | 10 hours | 5 hours | 11 hours | 5 hours | 4 hours | 13 hours |
| **iBP** | 70/55 | 95/50 | 125/55 | 51/42 | 105/60 | 62/37 | 119/75 |
| **Bloodwork upon arrival at our hospital** | Lactate 135<br>K 5.1<br>pH 7.26; $HCO_3$ 24 | Lactate 77<br>K 8.8<br>pH 6.96; $HCO_3$ 4.5 | Lactate 91<br>K 7<br>pH 7.08; $HCO_3$ 9.2 | Lactate 129<br>K 4.9<br>pH 7.17; $HCO_3$ 17.5 | Lactate 135<br>K 6.2<br>pH 7.02; $HCO_3$ 7.02 | Lactate > 135<br>K 4.4<br>pH 6.89; $HCO_3$ 4.4 | Lactate 88<br>K 4.9<br>pH 7.11; $HCO_3$ 18 |
| **24h lactate clearance** | | | | | | | |
| **ECG** | Normal | RBBB | TQS with peaked T | RBBB | RBBB | Normal | Normal |
| **Culture** | Negative | Negative | – | Negative | Negative | Negative | Negative |
| **Antibiotic therapy** | Piperacillin-tazob | Ceftriaxone | – | Piperacilina-tazob | Ceftriaxone | Piperacillin-tazob | Ceftriaxone + clarithromycin |
| **Treatment** | 5-day HDFVVC | Dialysis (AHT) + 2-day CVHDF | Dialysis | 24-hour CVHDF | 24-hour CVHDF | 6-day CVHDF | 24-hour CVHDF |
| **Amines** | Noradrenaline (2.35 µg/kg/min) + dopamina (4.4 µg/kg/min) | Noradrenaline (0.55mcg/kg/min) | – | Noradrenaline (1.78mcg/kg/min) + dopamine (13.3mcg/kg/min) | Noradrenaline (1.12mcg/kg/min) | Noradrenaline (2.95mcg/kg/min) | Noradrenaline (0.235mcg/kg/min) |
| **Ventilation** | OTI | NIMV | Spontaneous | OTI | OTI | OTI | Spontaneous |
| **Admission to ICU** | 7 days | 4 days | NO | 2 days (death) | 9 days | 9 days | 4 days |
| **T hospitalisation** | 16 days | 9 days | 7 days | 2 days | 15 days | | 11 days |

RBBB: right bundle branch block; DM2: diabetes mellitus type 2; ECG: electrocardiogram; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; GCS: Glasgow coma scale; BPH: benign prostatic hyperplasia; CVHDF: continuous veno-venous haemodiafiltration; AHT: arterial hypertension; OTI: orotracheal intubation; CRF: chronic renal failure; OSAHS: obstructive sleep apnoea-hypopnoea syndrome; T: time; BP: blood pressure; iBP: initial blood pressure; ICU: intensive care unit; NIMV: non-invasive mechanical ventilation.

## Case 4

A 78-year old female with type 2 diabetes on treatment with metformin at 850mg/24h, with hypertension, dyslipidaemia and a history of ischaemic stroke and cardiological follow-up for monitoring angina and functional class II dyspnoea (echocardiogram revealing apical wall motion abnormalities, mild ventricular dysfunction and left ventricular ejection fraction at 63%; coronary angiography was normal). Prior renal function was normal. The patient sought treatment at another hospital due to general discomfort with asthenia and weakness in the legs with 2 days evolution and episodes of diarrhoea. In the emergency department, the patient developed epigastric pain radiating to the back, haemodynamic instability, BP of 65/35, bradycardia at 35bpm, sweating and oligoanuria. The initial laboratory analyses are summarised in the Table 1. Notable results included severe metabolic acidosis with an elevated anion GAP. Sodium bicarbonate and dopamine perfusion were initiated. The patient was intubated due to respiratory failure and then transferred to our hospital. Upon arrival, the patient was haemodynamically unstable, with a BP of 51/42 and anuria; we started perfusion with noradrenaline and maintained the dopamine treatment. The laboratory analyses are summarised in the Table 1. We performed an emergency echocardiogram that revealed no significant abnormalities and a thoraco-abdominal CAT scan with no detected acute pathology. The patient was admitted to the ICU, where the metabolic acidosis was corrected and CVHDF was started. With poor evolution, the patient developed refractory multi-organ failure and died 36 hours after hospitalisation.

## Case 5

A 76-year old male, with type 2 diabetes and treatment with metformin at 850mg/24h and vildagliptin; the patient suffered from COPD and right nephrolithiasis diagnosed by haematuria and was on treatment with ibuprofen. Prior renal function was normal. The patient sought treatment at another hospital due to general discomfort and abdominal pain with three days evolution. The initial laboratory analyses are summarised in the Table 1. Notable results included severe metabolic acidosis, worsening renal function and severe hyperkalaemia. The patient rapidly progressed into respiratory failure, requiring orotracheal intubation. Treatment was started with sodium bicarbonate and the patient was transferred to our hospital. Upon arrival, the patient suffered from haemodynamic instability requiring high doses of noradrenaline; the laboratory analysis revealed worsening of metabolic acidosis and increased lactate levels. He was admitted to the ICU, where CVHDF was administered for 24 hours. The patient progressed quite favourably, with normalised laboratory parameters and no need for renal replacement therapy and was discharged 15 days after hospitalisation with an eGFR of 48ml/min/1.73m$^2$, under outpatient follow-up control.

## Case 6

A 52-year old male from Belgium was in Spain on vacation, with type 2 diabetes on treatment with metformin at 850mg/24h, with COPD and a history of smoking. Prior renal function was normal. The patient sought treatment at another hospital due to general discomfort and decreased level of consciousness with several hours' evolution. The patient apparently had also suffered diarrhoea during the last 24 hours. The initial laboratory analyses are summarised in the Table 1. Notable results included a Glasgow Coma Scale (GCS) of 10, severe hypoglycaemia at 49mg/dl, severe metabolic acidosis, acute renal failure with creatinine at 13.7mg/dl and severe hyperkalaemia. The patient was transferred to our hospital, where BP reached 110/70, with worsening metabolic acidosis and renal function, increased lactate, GCS of 13 and anisocoric photoreactive pupils. We administered sodium bicarbonate and took a cranial computed tomography, which ruled out intra-cranial pathology, with a later spontaneous reversal of anisocoria. The patient was unstable upon admission to the ICU, where perfusion with high doses of noradrenaline was started along with orotracheal intubation. CVHDF was also started along with antibiotic prophylaxis with piperacillin-tazobactam, with no increases in parameters of sepsis and negative culture results. Intoxication with methanol or ethylene glycol was ruled out at the same time as ethanol perfusion was started. This treatment was removed 12 hours after hospitalisation after laboratory tests ruled out the possibility of intoxication. The patient remained in a state of metabolic acidosis with lactate >135mg/dl and haemodynamic instability increased during the first 24 hours. After 36 hours, vaso-active amine treatment was reduced until fully suspended on the seventh day of hospitalisation. Later progression was favourable, with no need for renal replacement therapy; the patient was transferred back to Belgium after 13 days in our hospital, with a final creatinine value of 2.59mg/dl and an eGFR of 26ml/min/1.73m$^2$.

## Case 7

A 75-year old male, with allergy to aspirin, penicillin, and quinolones, had hypertension, asthma, type 2 diabetes and was on treatment with metformin at 850mg/24h. The patient sought treatment at his reference hospital due to general discomfort, fever and abundant vomiting. Initial laboratory values are summarised in the Table 1. Notable results included mild renal failure and metabolic acidosis. An abdominal ultrasound resulted normal and the patient was transferred to our hospital. Upon arrival in the emergency department, the patient had haemodynamic instability with undetectable BP and respiratory failure. We started the patient on low doses of perfused vasoactive amines. Given the patient's critical state, we performed a CAT scan, which yielded no pathological findings. The patient was then

admitted to the ICU, where treatment with low doses of vasoactive amines was continued. CVHDF was applied for 24 hours due to oligoanuria. Antibiotic treatment was started with ceftriaxone and clarithromycin, despite an absence of increase in sepsis parameters and negative culture results. The patient progressed favourably, with normalised laboratory values and no need for renal replacement therapy. The patient was discharged after 11 days in the hospital, with an eGFR>60ml/min/1.73m$^2$.

## DISCUSSION

Lactic acidosis can appear during treatment with metformin, although it has a low incidence rate; different studies report an incidence of 1-8 cases per 100 000 patients treated per year.[1-3] As in all of the cases described in our series, this condition normally develops with non-specific symptoms such as general discomfort, myalgia and abdominal symptoms (diarrhoea, nausea, and vomiting). Worsening renal function occurs as a result of dehydration and pharmacological nephrotoxicity caused by the accumulation of metformin due to reduced elimination by the kidneys (type B lactic acidosis). This condition is also defined by laboratory values included pH<7.35, bicarbonate <22mEq/l, lactate >5mmol/l and elevated anion GAP (Na – [HCO3 + Cl]>10-12). According to different studies,[4] MALA can produce lower blood pH levels than in cases of lactic acidosis of different origin.

Metformin is a drug in the family of biguanides, which has been used since 1950 in type 2 diabetes mellitus patients, with reduced mortality rates of up to 36% in obese patients,[5] and decreased morbidity and mortality due to cardiovascular pathologies.[4] Its hypoglycaemic effect is based on inhibition of hepatic gluconeogenesis, increased cellular use of glucose, decreased gastrointestinal absorption of glucose and reduced liver metabolism of lactate.[6] Metformin toxicity is based on its binding to the mitochondrial membrane and inhibiting oxidative phosphorylation, thus converting pyruvate into lactate. The half-life of metformin is 1.5-2 hours, it circulates freely (without binding to proteins) and is 90% eliminated by the kidneys. In situations of acute renal failure (eGFR<60ml/min/1.73m$^2$), the half-life of metformin increases, as does the risk of accumulation.[3]

Lactate is produced through the metabolism of pyruvate. Pyruvate is the ultimate result of glycolysis, and is finally transformed through the Krebs cycle into $CO_2$ and water or, in anaerobic situations, into lactate. Increased serum concentrations of lactate (>45mg/dl) can be due to increased production, decreased metabolisation, or alterations in cellular reduction pathways. Lactate concentrations can become elevated in situations of haemodynamic instability and tissue hypoxia (type A lactic acidosis), or when certain drugs become accumulated in the body (type B lactic acidosis).[2]

The relationship between lactic acidosis and metformin has been the subject of much debate,[4] but there does appear to be a causal relationship. Certain risk factors have been identified for developing MALA, such as acute renal failure, situations of hypoxemia such as sepsis, heart failure and respiratory failure, a previous history of lactic acidosis, liver disease,[4,6,8] and dehydration.[2] Precaution is recommended when using metformin in patients with an eGFR<60ml/min/1.73m$^2$, and it should not be used at all if GFR<30ml/min/1.73m$^2$.[1,9] In spite of these recommendations, a recent Cochrane review concluded that no clear evidence exists suggesting that metformin is associated with an increased risk of lactic acidosis in comparison with other hypoglycaemic treatments.[10] Two of our patients already had a glomerular filtration rate <45ml/min/1.73m$^2$ prior to the described episode, which already constitutes a contraindication for the use of metformin. In the other cases, prior gastrointestinal symptoms and pre-renal acute renal failure predisposed the patient for an accumulation of metformin, which favours the elevated production of lactate.

MALA has a very poor prognosis if it is not diagnosed and treated early.[4] The treatment of choice consists of suspending the drug and, since metformin is susceptible to dialysis, renal replacement therapy[2,5,11,12] using prolonged haemodialysis or CVHDF in the case of haemodynamic instability. This treatment corrects the acid-base imbalance, eliminates lactate and decreases metformin levels. Even so, recent studies carried out in the ICU report a mortality rate of 30%[5] that has been associated with elevated lactate levels.[4] In our study, patients with higher concentrations of lactate were those with a slower improvement, and one of these patients died (14.2%). Paradoxically, some studies, conclude that MALA has a better prognosis[4] despite lower pH levels than in other causes of lactic acidosis.

We believe that MALA is a severe disease that requires early diagnosis and treatment. Renal replacement therapy is not the solution for all patients, but it can improve the prognosis of severe cases if started early. We believe that the use of metformin should be limited in diabetic patients with altered renal function, despite the current level of controversy surrounding this treatment.

### Conflicts of interest

The authors state that they have no potential conflicts of interest related to the contents of this article.

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Sent to review: 9 Mar. 2012 | Accepted: 11 Jun. 2012