Netherlands
The Journal of Medicine

REVIEW

Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment

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ABSTRACT

Background: Lactic acidosis in metformin use is a widely recognised but rare side effect. Case reports usually describe elderly patients with conditions which in themselves can cause lactic acidosis or with known contraindications to metformin. We present cases of an elderly woman, a younger woman and a man who developed serious metformin-induced lactic acidosis in the absence of chronic renal impairment.

Results: Laboratory results showed acute renal failure in all patients. The pH was 6.77, 6.98 and 6.7, respectively, and lactate levels were 18.2, 18.4 and 11.7 mmol/l, respectively. Metformin plasma levels were 58, 57 and 39 mg/l. All patients received continuous veno-venous haemofiltration (CVVH), using bicarbonate as a buffer solution shortly after arrival on our ICU. In the subsequent hours, a steep decline in the plasma levels was observed, with a concomitant increase in pH. No other diagnoses were made, so we concluded that all patients were suffering from metformin-induced lactic acidosis. Despite the severity of the metabolic acidosis, both female patients survived. Our male patient died after a prolonged stay in the ICU, but this was not related to metformin.

Conclusion: Metformin-induced lactic acidosis does exist. Metformin-induced lactic acidosis may occur in patients with previously normal renal function, even in young patients. Patients with extreme (lactic) metabolic acidosis caused by metformin can survive when CVVH treatment is initiated rapidly. Intercurrent symptoms or diseases that affect renal perfusion can precipitate lactic acidosis.

KEYWORDS

Continuous veno-venous haemofiltration, lactic acidosis, metformin

INTRODUCTION

Metformin is a biguanide that is widely used in the treatment of type II diabetes mellitus. Its association with lactic acidosis is rare with an estimated incidence of 6.3 per 100,000 patient years.[1] Mortality is described as being about 50%.

Most reports describe cases of patients with concurrent conditions, such as advanced age, liver disease, alcoholism, cardiopulmonary disease or renal failure, which in themselves can cause lactic acidosis or metformin accumulation. Other reports describe self-inflicted or accidental overdose. We present three patients who all used metformin and developed serious lactic acidosis in the absence of chronic renal impairment.

CASE REPORTS

Patient A, a 45-year-old woman with a history of diabetes mellitus type II, mental retardation and bipolar disorder presented to the accident and emergency department (A&E) after she had collapsed at home and had not regained consciousness. She had been nauseous, with vomiting and experiencing diarrhoea for about a week. She was on metformin 500 mg three times daily and flupentixol 40 mg once every two weeks. At presentation, she was first suspected of having a neurological disorder. After computed tomography imaging of the brain showed no signs of brainstem infarction or basilaris thrombosis, lumbar puncture was performed and revealed no abnormalities. She became haemodynamically unstable, was intubated and transferred to our ICU where she was ventilated. Laboratory results showed renal failure and lactic acidosis (serum urea 30.8 mmol/l, serum creatinine 1177 µmol /l, pH 6.77, bicarbonate 5 mmol/l, and lactate

18.2 mmol/l). CVVH with a bicarbonate buffer solution was started three hours after hospitalisation. Dopamine and noradrenaline were continued for three days. Nine days after admission the CVVH was stopped, and she was extubated. Five days later she was transferred to a general medical ward where she needed no further renal replacement therapy. After six days on the ward she was discharged with normal renal function. Her creatinine was 77 µmol/l. On specific questioning, she reported taking all her medications as prescribed and denied an intentional overdose. This was confirmed by her parents.

Patient B, a 69-year-old woman, presented to the A&E complaining of drowsiness and hypoglycaemia. Her medical history included diabetes mellitus type II, multiple cerebral infarctions and cardiovascular disease. On admission she was on acetylsalicylic acid, carvedilol, furosemide, gliclazide, telmisartan, atorvastatin, insulin and metformin one gram three times daily. She had been experiencing nausea, vomiting and diarrhoea for a couple of days. On examination her airway was clear and secured, saturation was 99%, but ventilation was manually assisted, blood pressure could not be measured and her pulse was weak. She was given a total of 1.5 mg atropine, fluids and glucose intravenously. She remained comatose and bradycardic, and dopamine and isoprenaline were started. A cardiac arrest was treated with 1 mg of adrenaline and a short episode of cardiac massage. Laboratory results then revealed renal failure (potassium level of 9 mmol/l, serum urea 29.9 mmol/l, and serum creatinine 458 µmol/l). Blood gas analysis showed pH 6.98, bicarbonate 5.3 mmol/l, pO_2 7.7 kPa, pCO_2 3.08 kPa, and lactate 14.8 mmol/l. Still in a coma, she was taken to the ICU where she was intubated and ventilated. By then she had become anuric and CVVH with a bicarbonate buffer solution was started five hours after admission. Blood glucose levels had normalised. Further physical examination revealed only subtle pre-existing oedema on the lower legs. After CVVH was commenced her condition started to improve. Blood gas analysis was normal within 20 hours and one day later she regained consciousness. Three days after admission the CVVH was stopped and she could be extubated. After five days on our intensive care she was transferred to a general medical ward. She was discharged after another 14 days. Her haemodynamic and ventilatory status remained stable and she needed no further renal replacement therapy. Her creatinine concentration was 165 µmol/l.

Patient C, a 72-year-old man, with a history of type II diabetes mellitus, mild valvular heart and peripheral vascular disease and *Staphylococcus aureus* bacteriaemia presented to our A&E comatose and in respiratory distress. He had been experiencing gastrointestinal discomfort for days. Laboratory results showed renal failure and lactic acidosis (serum urea 50 mmol/l, serum creatinine 811 µmol /l, pH 6.70 and lactate 11.7 mmol/l). He was on metformin 1000 mg three times daily, tolbutamide, simvastatin, hydrochlorothiazide and enalapril. He was immediately intubated and transferred to the ICU where he was put on a noradrenaline infusion. Cultures remained negative and the cardiologist excluded the possibility of endocarditis. Six hours after hospitalisation, CVVH with bicarbonate buffer solution was started. After 30 days his intensive care stay had been complicated by catheter sepsis and ventilator-acquired pneumonia. He could not be extubated within 30 days of ICU stay. Eventually a tracheotomy was performed. Fifty days after admission he became haemodynamically unstable, developed an ileus and had progressive necrosis of his lower extremities. It was decided that further medical treatment would not be beneficial and he died after all therapies had been discontinued.

Regarding our patients' medication regimes it has to be noted that patients B and C were both on drugs that inhibit the renin-angiotensin-aldosterone system. These drugs are known to possibly cause renal function disorders. Both patients had been using these drugs for a longer period of time in which renal function had always been normal. Unfortunately, the exact duration of treatment with metformin in our patients prior to presentation at the emergency room was unknown.

DISCUSSION

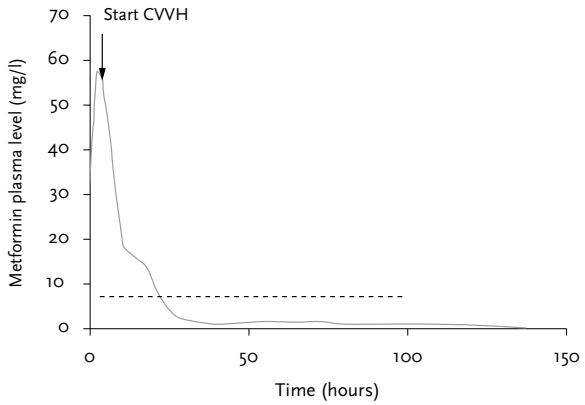
Pharmacokinetics of metformin

After oral intake, metformin has a maximum plasma level at 2.5 hours. When large amounts of metformin are swallowed, maximum plasma levels may appear later.[2] Protein binding of metformin is negligible. The mean volume of distribution is 63 to 276 litres. These two properties of metformin mean that haemodialysis or haemofiltration can effectively remove metformin from serum. Even low blood flow has appeared to be effective in removing metformin.[3] Metformin is not metabolised and mainly (90%) excreted by kidneys. Tubular secretion and glomerular filtration are considered the major routes of metformin elimination.[2] The blood elimination half-life is around 6.5 hours in patients with a normal renal function.[3] It is prolonged in patients with renal impairment. Reduction in creatinine clearance is proportional to reduction in metformin clearance.

In all patients plasma was taken to determine metformin levels; metformin was measured in plasma using liquid chromatographic-tandem mass spectrometry (LC-MS-MS), at the laboratory of the Department of Clinical Pharmacy

of the University Medical Centre Groningen. In the first hours after hospitalisation, the metformin plasma level increased twofold in patient A. An autointoxication was considered. Approximately three hours after the patient was hospitalised, CVVH was initiated. In the first eight hours of haemofiltration, around two-thirds of the metformin was eliminated and the pH improved from 6.77 to 7.25. Patient B presented with pH 6.98 and a metformin level of 57 mg/l. Approximately five hours after patient B was hospitalised, CVVH was instituted. In this case, metformin appeared to be cleared with a half-life of approximately 12.5 hours. During the first 20 hours of treatment, the pH improved from 6.98 to 7.41. Patient C presented with a pH 6.70 and a metformin level of 39 mg/l, which increased to 45 mg/l within the next four hours. CVVH was initiated three hours after admission to our ICU (two hours after the moment of first metformin measurement). Unfortunately no other measurements of metformin levels were done. His pH improved to normal within 31 hours. *Table 1* shows clinical parameters of all patients, *figures 1* and *2* show metformin levels. In all cases the metformin plasma levels appeared to be extremely high. In controlled clinical trials, maximum metformin plasma concentrations did not exceed 4 mg/l.[2] In our three patients CVVH succeeded in treating the extreme acidosis and stabilising the patients.

Figure 1. *Metformin plasma levels in patient A*



Therapeutic levels generally do not exceed 4 mg/l (dotted line). CVVH = continuous veno-venous haemo-filtration.

Pathophysiology of lactic acidosis

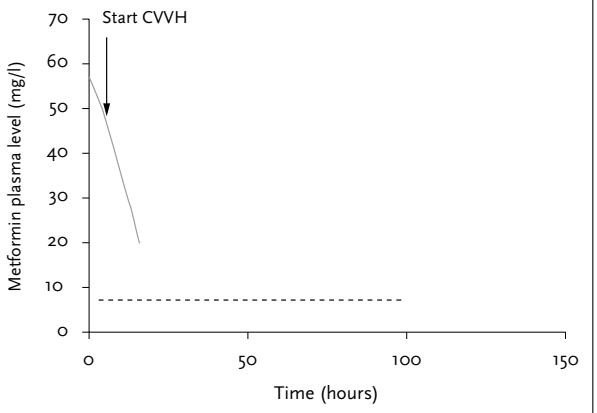
Lactic acidosis is a broad anion gap metabolic acidosis: pH <7.35 and lactate > 5 mmol/l.[4] Cohen and Woods[5] classified lactic acidosis into type A and type B. In general, type A lactic acidosis represents lactate overproduction: situations in which the body has to regenerate ATP in the absence of oxygen. Recently, both experimental and human studies have demonstrated that in situations comparable with hyperkinetic septic shock, skeletal muscle is a

Table 1. *Metformin plasma level, serum lactate and creatinine and pH following severe lactate acidosis*

Date	Time	Metformin plasma level (mg/l)	Creatinine (µmol/l)	Lactate (mmol/l)	pH
Patient A					
1-8-2006	13:59	32.6	1177		ND
	16:42	58.5	1098	18.2	6.77
	23:59	18.7	587	13.1	7.25
2-8-2006	08:00	14.3	356	3.9	7.30
3-8-2006	18:38	2.3	130	1.4	7.33
4-8-2006	08:34	1.4	136	ND	ND
5-8-2006	08:44	1	127	ND	ND
6-8-2006	08:56	1	146	ND	ND
7-8-2006	08:33	0	150	0.8	7.35
Patient B					
27-10-2006	12:48	ND	440	18.4	6.98
	16:00	57	358	12.3	7.20
	20:00	50	314	7.7	7.29
28-10-2006	08:00	20	161	2.7	7.41
29-10-2006	08:00	ND	142	ND	ND
Patient C					
22-2-2007	13:15	ND	811	11.6	6.70
22-2-2007	16:00	39	ND	13.7	7.00
22-2-2007	20:00	45	ND	10.6	6.96
23-2-2007	02:00	ND	ND	15.4	7.27
23-2-2007	08:00	ND	423	8.9	7.28
23-2-2007	20:30	ND	345	3.4	7.38

ND = not done.

Figure 2. *Metformin plasma levels in patient B*



Therapeutic levels generally do not exceed 4 mg/l (dotted line). CVVH = continuous veno-venous haemo-filtration.

leading source of lactate production by exaggerated aerobic glycolysis through Na^+/K^+ /ATP-ase stimulation.[6] This creates a hyperlactataemia that is not mainly caused by hypoxia. Type B lactic acidosis represents underutilisation of lactate and involves impaired removal of lactic acid by oxidation or gluconeogenesis. So, high lactate production can be caused by aerobic or anaerobic causes. Furthermore, a decrease in lactate clearance may contribute to high lactate levels.

Lactic acidosis and metformin

For about 40 years, metformin has been used in the treatment of diabetes mellitus type II. The UK Prospective Diabetes Study Group provided evidence that metformin reduced the risk of morbidity and death in treatment of diabetes mellitus type II.[7] Known side effects are nausea, anorexia, and diarrhoea and lactic acidosis. In order to record the incidence of fatal and nonfatal lactic acidosis per patient-year, Salpeter *et al.*[1] reviewed all studies of metformin treatment from 1966 up to August 2005. Their data revealed no cases of fatal or nonfatal lactic acidosis. Also, there was no difference in lactate levels between metformin and placebo or other treatment groups. They concluded that there is no evidence that metformin is associated with an increased risk of increased lactate levels or lactic acidosis. Nevertheless, over the last years, several case reports have been published on the association between metformin and lactic acidosis. Lalau and Race[8] suggested the link between metformin and lactic acidosis should be carefully referred to as metformin-unrelated, metformin-associated (metformin and concurrent pathologies as co-precipitating factors of lactic acidosis) or metformin-induced (metformin as the only precipitating factor). To be able to distinguish between the terms suggested by Lalau and Race and to make data more comparable, at the very least reports should publish metformin levels, serum creatinine levels, arterial lactate levels, history of concurrent pathologies and a clear context of the case.

The pathogenesis of metformin-associated lactic acidosis is not completely understood. Metformin has affinity for the mitochondrion membrane.[9,10] Due to this affinity, metformin affects the electron transport (NADH concentration increases) and thereby inhibits oxidative metabolism. Especially when metformin levels are high, oxidative phosphorylation is reduced and aerobic metabolism switches to anaerobic metabolism. Metformin can also delay or decrease gastrointestinal glucose absorption, hepatic gluconeogenesis, and increase intestinal lactate production and peripheral insulin-related glucose reuptake.

Metformin accumulation

Since metformin clearance is mainly renal, it seems logical to expect metformin accumulation in high serum creatinine levels in oliguric or anuric patients. However, in Stades' case series,[11] the severity of renal failure expressed as serum creatinine levels neither correlated with lactate levels nor with metformin levels. Other mechanisms of metformin accumulation have been suggested. One case report describes metformin accumulation in a patient with intestinal obstruction due to volvulus in the absence of renal failure.[12] An animal experiment used to examine the relationship between metformin levels and intestinal obstruction indeed showed metformin retention but no accumulation or lactic acidosis.[12] In cases where lactic acidosis is accompanied with high serum creatinine levels, the plasma concentration of metformin is not necessarily abnormally high. On the other hand patients with previously normal renal function and acute renal failure in the A&E can have high metformin levels. The latter situation could suggest that renal failure had a gradual onset. Metformin levels do not have to be extremely high to cause lactic acidosis. But once lactic acidosis has commenced, it can cause or aggravate any organ failure. Onset of renal failure and last intake of metformin seem essential in determining whether renal failure is primary or secondary to concurrent conditions precipitating lactic acidosis. Metformin levels are important in the context, but do not predict outcome.

Treatment of lactic acidosis in metformin use

The mainstay of treatment involves repairing acid-base balance, removing causes of lactic acidosis and supportive therapy. Haemodialysis with bicarbonate replacement fluid has been used successfully in the treatment of lactic acidosis in metformin use. Haemodialysis not only corrects the acidosis but also efficiently removes metformin from plasma,[13] preventing further lactate overproduction and

removes lactate. Although haemofiltration is thought to treat lactic acidosis (regardless of metformin use), kinetic studies of lactate removal, however, suggest that removal can not significantly counteract lactate production.[14] In haemodynamically unstable patients, continuous renal replacement therapy (CRRT) does the same things more gradually than conventional haemodialysis and could therefore be considered preferable. A disadvantage compared with conventional haemodialysis could be the relatively slower clearance rate.[15] Activated charcoal can absorb metformin and prevent absorption by the intestines so it is recommended in treating metformin overdose. Sodium bicarbonate or dichloroacetate are controversial treatments.

We have presented three patients who developed lactic acidosis in the absence of other causes of lactic acidosis. We have emphasised their previously normal renal function. Several reports have also described patients with previously normal renal function and a pH less than 7.00. Stades *et al.*[11] published data of 47 cases of metformin use and lactic acidosis. Of those 47 patients, eight had no history of chronic renal failure, had a pH less than 7.00 and survived. Of these eight, all had acute renal failure, two had a history of cardiovascular disease, two had been given contrast fluid intravenously, four were in shock, one had a history of alcoholism, one had a history of COPD and two had sepsis on admission.

In our series, all patients had been suffering from gastrointestinal symptoms prior to admission. These symptoms could have been side effects of metformin or first signs of a developing lactic acidosis. Moreover, these symptoms could have deteriorated their previously normal renal function by dehydration. They all had acute renal failure, were haemodynamically unstable and in respiratory distress. Since there were no other reasonable explanations for lactic acidosis, in all patients a diagnosis of metformin-induced lactic acidosis was made.

In all three cases it is likely that due to pH alterations caused by elevated lactate, metabolism changed and negative effects of metformin accumulated. Changes in acid-base balance probably caused the deterioration. They all had high metformin levels, which could have been a sign of gradual onset of lactic acidosis and relatively acute renal failure.

Even though our patients did not experience chronic renal failure, their acute reversible prerenal failure prior to hospital admission, combined with ongoing use of metformin, could have caused a series of events eventually leading to metformin accumulation and lactic acidosis.

Our series is in accordance with the hypothesis that neither the level of lactate nor the level of plasma metformin predicts outcome.[11,16] Serum creatinine does not necessarily appear to be associated with metformin levels or outcome either. Our two female patients had normal renal function before admission, acute renal failure on presentation and improved renal function after discharge.

As mentioned, our patients all experienced gastrointestinal discomfort prior to their deterioration. We would like to emphasise the importance of giving patients full information about this side effect. Gastrointestinal symptoms could be the very first sign of developing lactic acidosis and should therefore be closely monitored. Physicians who prescribe metformin should instruct their patients to immediately report the onset of gastrointestinal discomfort. Patients who have been using metformin without side effects and start to develop gastrointestinal discomfort should stop taking metformin until the symptoms have disappeared. Moreover, the presence of any intercurrent disease that may affect renal perfusion should alarm doctors to temporarily stop metformin and/or any drug that influences renal function.

CONCLUSION

Lactic acidosis in metformin use is not only a problem in patients with pre-existing risk factors. In fact, by definition, metformin-induced lactic acidosis is diagnosed in the absence of other causes of lactic acidosis. Neither metformin levels, nor lactate levels, nor creatinine levels seem to predict outcome in lactic acidosis in metformin use. Patients with previously normal renal function and younger patients with no other comorbid conditions at all can develop metformin-induced lactic acidosis. Gastrointestinal discomfort or any intercurrent disease that affects renal perfusion in patients using metformin could precipitate lactic acidosis. CVVH can be a very successful treatment when started aggressively and rapidly, even in patients who have pH levels far below 7.0 and are unstable.

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