

## CASE REPORT

# Treatment of metformin-induced lactic acidosis

EA Verrij<sup>1</sup>, AMJ Wassink<sup>1</sup>, VHM Deneer<sup>2</sup>, O de Weerd<sup>1</sup>, ABM Geers<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, the Netherlands.

<sup>2</sup>Department of Clinical Pharmacology, St. Antonius Hospital, Nieuwegein, the Netherlands.

**Abstract.** Lactic acidosis is a rare but severe and life threatening side effect of metformin. As long as contraindications to its use are kept in mind, metformin can be prescribed safely. If a patient develops one of these contraindications while on metformin therapy (e.g. renal insufficiency), metformin therapy should be discontinued temporarily, because the likelihood of developing metformin-induced lactic acidosis is then significantly increased. In metformin-induced lactic acidosis renal replacement therapy is an effective treatment option, because it eliminates metformin from the circulation and corrects the acidosis. In renal insufficiency it is important to continue dialysis despite normalized plasma metformin levels, to finally eliminate metformin that is stored in the deep tissue compartments.

## Introduction

Type 2 diabetes mellitus is a common disease which is becoming more prevalent. Metformin, a blood glucose lowering drug, is frequently used in the treatment of type 2 diabetes mellitus. Lactic acidosis is a rare but serious side effect in patients treated with metformin [1]. The likelihood of metformin-induced lactic acidosis is increased especially in patients with renal insufficiency, since metformin clearance is renal. In this article we describe two patients with metformin-induced lactic acidosis following deterioration of renal function. Furthermore, we will discuss the pathogenesis and the treatment of metformin induced lactic acidosis.

## Case 1

Patient A, a 77-year-old woman, was referred to our emergency department by her general practitioner with dehydration caused by diarrhoea and vomiting. Her prior medical history revealed a myocardial infarction four years previously, hypertension, and type 2 diabetes mellitus. She used metformin 850 mg three times daily and glibenclamide 5 mg three times daily. She had watery stools, was nauseous and had been vomiting for five days. She had not eaten or drunk much, however, she had taken her medication as prescribed. In the last few hours before presentation her physical condition had deteriorated. At the emergency department we saw a confused and restless woman. Blood pressure was 132/98 mmHg, pulse 98/min, temperature 33.8 degrees Celsius. Her skin was cold and skin turgor was decreased. She was hyperventilating. Heart, lungs and abdomen were without abnormalities. Arterial blood gas analysis showed (reference values in brackets) pH 6.84 (7.35-7.45), PaCO<sub>2</sub> 1.7 kPa (4.7-6.4), PaO<sub>2</sub> 17 kPa (10-13), HCO<sub>3</sub><sup>-</sup> 2.1 mmol/l (22-29). Additional laboratory tests: CRP 63 mg/l (<5), leucocytes 14.7 g/l (2.5-8.2 g/l), differentiation of leucocytes with no abnormalities, urea 23.6 mmol/l (2.5-6.4), creatinine 616 micromol/l (50-105) (2 years earlier:126), lactate 21.1 mmol/l (0.5-2.2), glucose 13 mmol/l (<11), anion-gap 43 mmol/l (12 ± 2), and no ketonuria. Because we suspected metformin-induced lactic acidosis, a bicarbonate infusion was given to

**Table 1. Contra-indications for metformin use**

Renal failure or renal dysfunction (serum creatinin > 135 micromol/l in men and > 110 micromol/l in women)
Acute conditions that are likely to change renal function (e.g. dehydration, severe infections, shock, intravascular administration of a contrast agent containing iodine*)
Acute or chronic conditions that can induce tissue hypoxia (e.g. heart failure, pulmonary insufficiency, shock, a recent myocardial infarction)
Liver insufficiency
Ketoacidosis, diabetic precoma
Acute alcohol intoxication, alcoholism
Breast feeding and pregnancy
Surgery*

\* If a contrast agent containing iodine is to be administered or if elective surgery is to be carried out, metformin therapy should be stopped 48 hours beforehand. Metformin therapy can be restarted 48 hours later, but only if renal function has returned to normal.

the patient and she was admitted to the intensive care unit. Shortly after admission she became haemodynamically unstable (blood pressure 80/40 mmHg). She was intubated and intravenous inotropy (dobutamine, dopamine) and noradrenalin was started. Her CVP was 10 and oxygen saturation after intubation was 99%. In addition, continuous venovenous haemofiltration (CVVH) with a bicarbonate buffer solution was started to eliminate metformin from the circulation. During CVVH treatment lactate levels slowly decreased and acid-base balance gradually improved. Despite maximum therapy, blood pressure levels continued to decrease and 38 hours after admission our patient died. The serum metformin level on presentation was determined retrospectively and was 58 mg/l (normal values during the use of metformin: 1-2 mg/l). Furthermore her blood and urine cultures remained negative.

## Case 2

Patient B, a 69-year-old woman, was referred to our emergency department by her general practitioner, because he thought her symptoms were due to pneumonia. Her medical history revealed type 2 diabetes mellitus and mild renal insufficiency (3 years earlier: creatinine 138 mmol/l). She used metformin 850 mg twice daily and glimepiride 6 mg once daily, enalapril, furosemide and had been taking diclofenac (NSAID) for a few days. She was nauseous and had vomited. At our

## Correspondence:

E.A.Verrij  
Email: e.verrij@antonius.net

emergency department we saw a lethargic woman with a blood pressure of 100/70 mmHg, pulse 100/min, temperature 32.6 degrees Celsius. Further physical examination revealed no abnormalities. Arterial blood gas analysis showed: pH 6.81 (7.35-7.45), PaCO<sub>2</sub> 1.5 kPa (4.7-6.4), PaO<sub>2</sub> 32.8 kPa (10-13), HCO<sub>3</sub><sup>-</sup> 1.7 mmol/l (22-29). Additional laboratory tests: urea 22.1 mmol/l (2.5-6.4), creatinine 998 micromol/l (50-105), CRP 63 mg/l (<5), leucocytes 12.8 g/l (2.5-8.2 g/l), differentiation of leucocytes without abnormalities, lactate 23.8 mmol/l (0.5-2.2), anion-gap 31.3 (12 ± 2). A plain X-ray of the thorax showed no abnormalities. We suspected metformin-induced lactic acidosis, caused by severe renal insufficiency due to dehydration and the use of NSAIDs. Our patient was admitted to the intensive care unit where she was intubated and ventilated mechanically. During admission, intravenous noradrenalin was started because of haemodynamic instability. CVVH with a bicarbonate buffer solution was started a few hours after admission. This induced acid-base balance normalization, furthermore it led to metformin removal from the circulation (Figure 1). After two days our patient was extubated, and a few days later she was transferred to the ward where she remained dependent on haemodialysis due to acute tubular necrosis. During hospitalization, blood and urine cultures remained negative. Twenty days after admission she was discharged in a reasonable condition, at which time she was no longer dependent on haemodialysis.

## Discussion

Lactic acidosis is a rare but serious side effect of metformin therapy. The estimated mortality is 50% [1]. Metformin and phenformin are biguanides, and were introduced in the late 1950s [1]. Phenformin was withdrawn from clinical use in many countries in the 1970s because of the high risk of lactic acidosis. This risk is 40-64 cases per 100 000 person-years. The risk of lactic acidosis in patients using metformin is 10-20 times lower and is 0-8.4 cases per 100 000 person-years [2]. Nowadays, metformin is the only biguanide in use [3].

Metformin has a blood glucose lowering effect. This effect is caused by improved peripheral insulin sensitivity, improved peripheral glucose uptake, and reduced glucose production by the liver (gluconeogenesis) [4]. During gluconeogenesis, the liver can (in normal circumstances) convert lactate into water and carbon dioxide or glucose [5].

The pathogenesis of a metformin-induced lactic acidosis is complex and not completely understood. Metformin stimulates the non-oxidative glucose metabolism in the intestines, this increases local lactate production, which results in increased lactate levels in the portal circulation. These increased portal lactate levels decrease the pH of the liver, which causes a diminished lactate metabolism. Furthermore, metformin inhibits gluconeogenesis, this decreases the conversion of lactate into water and carbon dioxide or glucose by the liver. These mechanisms can cause accumulation of lactate in metformin intoxication [2,13].

There are two types of lactic acidosis: type A which is caused by tissue hypoxia and type B caused by overproduction or diminished clearance of lactate despite adequate tissue oxygenation. Metformin-induced lactic acidosis is a type B lactic acidosis. Within a few hours, type B lactic acidosis can turn into mixed type lactic acidosis (both types A and B), because the cardiac- and haemodynamic effects of a severe type B acidosis can cause haemodynamic instability [6], resulting in tissue hypoxia. In the two cases described here, metformin-induced lactic acidosis developed as a result of deterioration

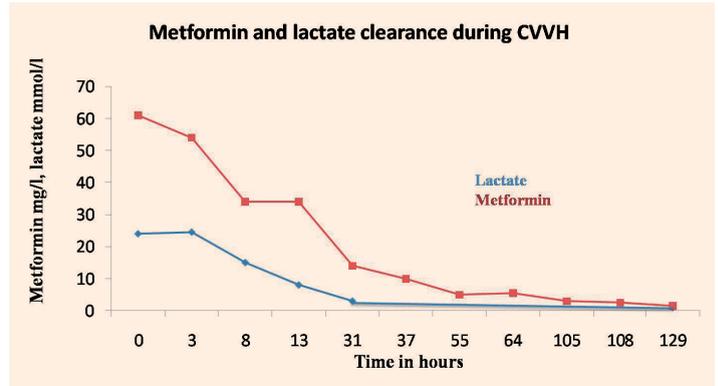


Figure 1. Metformin and lactate levels during CVVH.

of renal function. Eventually, both patients developed mixed type lactic acidosis due to haemodynamic instability.

In both our patients renal function deteriorated. Since metformin is cleared renally, metformin therapy should have been discontinued. Other contraindications to metformin therapy are shown in Table 1 (<http://www.cvzkompassen.nl/fk>). One in four patients prescribed metformin have contraindications to its use. Furthermore, the development of one of these contraindications rarely results in discontinuation of metformin therapy [7]. Fortunately, lactic acidosis is an uncommon phenomenon during metformin therapy [8, 9]. However, several case reports of metformin auto-intoxication prove that metformin overdose actually can induce lactic acidosis [10, 11, 12, and 13].

The estimated mortality of metformin-induced lactic acidosis is about 50% [1]. Prognosis is not related to serum metformin level, it is the patient's co-morbidity that seems to predict survival [14].

In the medical literature, haemodialysis is recommended as the treatment of choice in metformin-induced lactic acidosis [15]. Haemodialysis removes metformin from the circulation and corrects acidosis. Haemodynamically unstable patients, who cannot undergo haemodialysis can be treated by CVVH, because fluid exchange is slower [11]. The correct choice of replacement and dialysate fluids is important as conventional fluids contain lactate as a buffer, which may aggravate acidosis in cases of decreased capacity to metabolize lactate (e.g. in acidaemia or liver insufficiency) [11]. The use of a bicarbonate buffer solution in dialysis seems advantageous. It not only removes metformin from the circulation, but it also helps to correct the acidosis [16, 17]. There is little medical literature on metformin clearance during dialysis. Normal total clearance of metformin is 441 ml/min (half life 1.5 hours). In diminished renal function i.e. a glomerular filtration rate of 20-50 ml/min, total clearance is only 88.4 ml/min (half life 4.9 hours) [18]. In patient B, the volume of distribution was 0.5 l/kg and the patient's creatinine clearance prior to dialysis, was 20-50 ml/min [18]. We estimated a metformin clearance during haemodialysis of 31 ml/min. The half life time of metformin was 15 hours. There are only two other reports in medical literature, in which metformin clearance was estimated in metformin-induced lactic acidosis. Lalau et al. reported on a patient with renal insufficiency who underwent haemodialysis with a bicarbonate buffer solution. The estimated clearance was 68 ml/min [15]. Barrueto et al. reported on a patient who underwent CVVH because of auto-intoxication with metformin. In this case the estimated clearance was 50.4 ml/min [19]. The metformin clearance estimated in our patient

seems to be low (31 ml/min). However, the patient reported by Lalau et al. underwent haemodialysis in which fluid exchange is faster and therefore metformin clearance is higher. In auto-intoxication, as reported by Barrueto et al., metformin has not yet accumulated in the deeper tissue compartments, as seems to be the case in patients with renal insufficiency on chronic metformin therapy [15]. In patients with renal insufficiency there is a continuous release of metformin from these deeper tissue compartments into the circulation. This is why it is very important to continue dialysis in patients with renal insufficiency, even though plasma metformin levels have normalized. The duration of dialysis in metformin-induced lactic acidosis is not clear from the literature. In patient B the metformin level normalized in 105 hours, but dialysis (CVVH) was continued because of renal insufficiency.

## Conclusion

Lactic acidosis is a rare but severe and life threatening side effect of metformin. As long as contraindications are kept in mind, metformin can be prescribed safely. If a patient develops one of these contraindications while on metformin therapy (e.g. renal insufficiency), metformin therapy should be discontinued temporarily, because the likelihood of developing metformin-induced lactic acidosis is then significantly increased. In metformin-induced lactic acidosis renal replacement therapy is an effective treatment option, because it eliminates metformin from the circulation and corrects the acidosis. In renal insufficiency it is important to continue dialysis despite normalized plasma metformin levels to finally eliminate the metformin that is stored in the deep tissue compartments.

## References

- Bailey CJ, Turner RC. Metformin. *N Engl J Med.* 1996;334(9):574-579.
- Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care.* 1999;22(6):925-927.
- Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):854-865.
- Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs.* 2003;63(18):1879-1894.
- Devlin TM. *Textbook of biochemistry with clinical correlations.* Fifth ed. Wiley-Liss; 2002.
- Cohen RD, Woods HF. Metformin and lactic acidosis. *Diabetes Care.* 1999;22(6):1010-1011.
- Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med.* 2002;162(4):434-437.
- Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD. Contraindications to metformin therapy in patients with Type 2 diabetes; a population-based study of adherence to prescribing guidelines. *Diabet Med.* 2001;18(6):483-488.
- Holstein A, Nahrwold D, Hinze S, Egberts EH. Contraindications to metformin therapy are largely disregarded. *Diabet Med.* 1999;16(8):692-696.
- Lacher M, Hermanns-Clausen M, Haeffner K, Brandis M, Pohl M. Severe metformin intoxication with lactic acidosis in an adolescent. *Eur J Pediatr.* 2005;164(6):362-365.
- Teale KF, Devine A, Stewart H, Harper NJ. The management of metformin overdose. *Anaesthesia.* 1998;53(7):698-701.
- Chang CT, Chen YC, Fang JT, Huang CC. Metformin-associated lactic acidosis: case reports and literature review. *J Nephrol.* 2002;15(4):398-402.
- Pont de AC, Kerver ED, Jansen ME, Bijleveld YA, Franssen EJ, Hoekstra JB. A fatal auto-intoxication with metformin. *Ned Tijdschr Geneesk.* 2007;151(17):981-984.
- Lalau JD, Race JM. Lactic acidosis in metformin therapy. *Drugs.* 1999;58 suppl 1:55-60.
- Lalau JD, Andrejak M, Moriniere P, Coevoet B, Debussche X, Westeel PF, et al. Hemodialysis in the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. *Int J Clin Pharmacol Ther Toxicol.* 1989;27(6):285-288.
- Heaney D, Majid A, Junor B. Bicarbonate haemodialysis as a treatment of metformin overdose. *Nephrol Dial Transplant.* 1997;12(5):1046-1047.
- Lalau JD, Westeel PF, Debussche X, Dkissi H, Tolani M, Coevoet B, et al. Bicarbonate haemodialysis: an adequate treatment for lactic acidosis in diabetics treated by metformin. *Intensive Care Med.* 1987;13(6):383-387.
- Sirtori CR, Franceschini G, Galli-Kienle M, Cighetti G, Galli G, Bondioli A, et al. Disposition of metformin (N,N-dimethylbiguanide) in man. *Clin Pharmacol Ther.* 1978;24(6):683-693.
- Barrueto F, Meggs WJ, Barchman MJ. Clearance of metformin by hemofiltration in overdose. *J Toxicol Clin Toxicol.* 2002;40(2):177-180.