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Full Length Research Paper

Life-threatening lactic acidosis: Always a lost case? Key clues to the correct diagnosis: A case report

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Lactic acidosis is a severe condition with a high mortality rate. We report a case of near-fatal lactic acidosis, secondary to an acute kidney injury in a patient on chronic treatment with metformin. In this case, fast recognition and adequate treatment of the entity lead to rapid recovery of the patient. The differences in presentation of type A and type B lactic acidosis are emphasized, because of the importance for treatment and prognosis. Considerations and new insights in the mechanism of Metformin Associated Lactic Acidosis(MALA) are discussed.With this case report we want to point out the aspects one should consider when treating or stop treating a patient with metformin and nuance the fear for MALA.

Key Words: Severe Lactic Acidosis, Metformin Associated Lactic Acidosis, Metformin, Acute Kidney Injury, Case Report.

INTRODUCTION

Severe lactic acidosis is a serious condition frequently seen on the intensive care unit and is associated with a high mortality rate. Lactic acidosis is defined as a serum lactate level above 5 mmol/L and a pH less than 7.35. The serum lactate is the result of the balance of lactate production and lactate clearance. Disruption of the lactate metabolism can be caused by hypoxemia or impaired tissue perfusion, as typically present in patients with septic or cardiogenic shock. This is in the original Cohen-Woods classification denominated as type A lactic acidosis (Cohen and Woods, 1976). Lactate metabolism can also be altered by nonhypoxic causes such as administration of certain medications (e.g. metformin, salicylate, isoniazid and zidovudine), presence of certain cancers (e.g. lymphoma and leukemia) or ingestion of toxic substances (e.g. methanol, ethyleenglycol, salicylates, and paraldehyde). These causes are designated as type B lactic acidosis. In addition to the initiating underlying cause of lactic acidosis, tissue hypoxia can often also be partially attributed to the effect of acidosis on itself, as it results in decreased myocardial contraction, decreased response to vasopressors due to a down regulation of β-receptors and impaired calcium signalling, and negative effects on endothelial function and the inflammatory response (Kellum et al., 2004; Marsch et al., 2012; Crimi et al., 2012).These effects explain why lactic acidosis often causes a negative downward spiral of events.

Lactate on itself is not a toxic molecule, and does not cause acidosis; it is rather a reflection of the metabolic condition of a cell, asit is the consequence of intracellular acidosis (Kellum et al., 2004). As a consequence, hyperlactatemia indicates important alterations in the hemodynamic status and from observational data it is associated with increased mortality (Husain et al., 2003). In the published series of Husain et al. (2003), the mortality rate of lactic acidosis in an intensive care population was 83%. Another cohort study found a mortality rate of 100% in patients with severe lactic acidosis, defined as a pH lower than 7.00 (Friesecke et al., 2010). Nevertheless, a timely and correct diagnosis can in some cases lead to a very efficient treatment.

We describe the case of a patient presenting with a life-threatening profound lactic acidosis, which was rapidly recognized to be associated with metformin accumulation and was effectively treated with dialysis.

We want to underline the different presentation and course of disease of Metformin Associated Lactic Acidosis(MALA). We believe that this case report is interesting for two reasons: first because it indicates that

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a fast and correct differential diagnosis of profound lactic acidosis can be life saving; second, although MALA is associated with a high mortality, it is infrequent and almost always associated with an underlying condition. This case exemplifies that the fear for MALA is exaggerated in the literature, and leads to the unnecessary withholding of a potentially efficacious medication to a wide group of patients.

CASE REPORT

A 63-year old woman was brought to the emergency department because of nausea and pain in the lumbar region. She had been feeling ill for 3 days, and self-administered non-steroidal anti-inflammatory drugs to treat the pain. Since then, she was anuric for which she took bumetanide. When admitted, she was drowsy but responded adequately. She had a blood pressure of 89/43 mmHg, a pulse rate of 112 beats per minute, a peripheral saturation of 98% and a respiratory rate of 28 per minute. On clinical examination there were no abnormalities except a tender abdomen but without rebound tenderness, and both kidney regions were painful when palpated. A blood gas analysis revealed a metabolic acidosis with an arterial pH of 6.58 and lactate of 16.65 mmol/L. The pCO2 was 16 mmHg and the blood glucose was 178 mg/dL, bicarbonate was less than 2 mmol/L. The patient had a history of type 2 diabetes and a gastric sleeve operation 3 months before admission because of morbid obesity. The serum creatinine level in previous laboratory reports was normal. She was chronically treated with metformin 850 mg twice daily, pantoprazole 40 mg and acetylsalicylic acid 80 mg. She did not smoke nor used alcohol, and there was no history of ingestion of possible toxins.

Her laboratory findings are listed in table 1. We noted an acute kidney injury with a creatinine of 9,9 mg/dL and a serum potassium of 6 mmol/L. There was leukocytosis but the C-reactive protein was low. The electrocardiogram showed a sinusrhythm with normal QRS duration and normal ST segments, but peaking T-waives. An urgent CT abdomen was performed, which showed an obstructive lithiasis in the left ureter with hydronephrosis and rupture of the left pyelum, and a smallatrophic kidney on the right side.

The patient was started on norepinephrine, aggressive rehydration and bicarbonate infusion. She was transferred to the intensive care unit where continuous venovenous hemodialysis was initiated. The drowsiness improved markedly every hour and the norepinephrine dose was rapidly reduced and stopped. After 8 hours, the pH was 7.02 and the lactate was 5.5 mmol/L. Dialysis was stopped and a double J stent was placed in the left ureter to relieve the obstruction. Diuresis recommenced after this procedure, and creatinine levels dropped. The day after admission, she was discharged to the nephrology department. In follow-up, the patient developed a chronically impaired kidney function, the serum creatinine stabilized at 1.4 mg/dL.

DISCUSSION

Metformin has been the first line treatment of type 2 diabetes for over 50 years. It has proven to reduce cardiovascular morbidity and mortality (Ekström et al., 2012).Besides this, it has shown beneficial effects in hepatic steatosis, inflammation, cancer and polycystic ovary syndrome and exerts a protective effect on diabetic nephropathy (Garinis et al., 2010; Libby et al., 2009; Jayasena and Franks, 2014; Lalau et al., 2014). Historically, its use has been contra-indicated in conditions such as chronic kidney disease, congestive heart failure, chronic liver disease or periods of dehydration because of the fear of developing lactic acidosis, although it continues to be widely prescribed even in those conditions. More recent insights seem to confirm that even in these presumed contra-indications, metformin can be prescribed, and the advantages still outweigh the potential dangers (Lalau et al., 2014).

The relationship between metformin and lactic acidosis is complex and still not fully elucidated. Metformin is thought to cause lactic acidosis by reducing gluconeogenesis and glycogenolysis, inhibiting oxygen consumption and impairing mitochondrial function in the liver and other organs(Lalau, 2010). Cells try to compensate this by accelerating the glycolytic flux and consequently release lactate in the circulation (Lalau et al., 2014). However, the relationship between metformin accumulation, hyperlactatemia and lactic acidosis is still not completely understood. It has been hypothesized that metformin might have a protective role in shock, because of its beneficial effects on the vasomotility and the respiratory chain complex (Batandier et al., 2006). This can be one of the reasons why there is a higher survival rate of MALA as compared to other causes of lactic acidosis. In the case series of Friesecke et al. (2010), there were no survivors in the metformin-independent severe lactic acidosis (pH < 7.00) but patients with MALA had a survival rate of 50% even when severe acidosis was present. This was confirmed in the series of Kajbaf and Lalau (2013) where the survival rate of severe metformin-associated lactic acidosis was 53%. Accurate assessment of the incidence of MALA is difficult. From observational data and retrospective studies, the incidence number varies between 4.3 and 9.7 cases per 100 000 patient-years, an incidence not significantly different from that of lactic acidosis in non-metformin users (Salpeter et al., 2010). Therefore, it is important to consider that different forms of lactic acidosis should be distinguished in patients presenting with lactic acidosis and on chronic metformin treatment: the metformin intake can be the primary cause of the lactic acidosis, it can be

Table 1. Laboratory data.

Variable	*Value on admission*	*Unit*	*Reference Range Adults*
Hemoglobin	12,4	g/dL	11,8-14,8
White-cell count	20.73	10E3/µL	3.65-9.30
Platelet count	323	10E3/µL	171-374
Prothrombin time	48	%	70-120
Activated partial-thromboplastin time	42	Sec	28.9-38.1
Sodium	135	mmol/L	135-144
Potassium	6.1	mmol/L	3.6-4.8
Chloride	86	mmol/L	98-106
Calcium	2.44	mmol/L	2.12-2.62
Magnesium	1.29	mmol/L	0.70-1.05
Phosphorus	5.46	mmol/L	0.80-1.45
Osmolality	332	mOsm/kg	280-301
Glucose	176	mg/dL	82-115
Urea	176	mg/dL	13-43
Creatinine	9.94	mg/dL	0.55-0.96
Lactate	16.65	mmol/L	0.9-1.8
LDH	273.7	U/L	105-233
Lipase	229	U/L	0-60
C-reactive protein	40.1	mg/L	<5.0
Metformin	50.0	µg/mL	Therapeutic: 1-4 Toxic: 45-70
Arterial blood gas analysis			
pH	6.56		7.35-7.45
pCO2	14.7	mmHg	32-45
pO2	162.7	mmHg	83-108
Bicarbonate	1.3	mmol/L	22-26
Base excess	-37.5	mmol/L	-2 +3
Oxigen saturation	95.6	%	94-98

an innocent bystander (coincidental) or be co-responsible for the lactic acidosis. Our patient developed a lactic acidosis due to the acute kidney injury, itself caused by the obstruction of a functionally unique kidney, and the subsequent metformin accumulation. The initial differential diagnosis of lactic acidosis includes hypoxic causes or type A lactic acidosis and non-hypoxic causes or type B lactic acidosis. A remarkable finding in our case was the extreme acidosis and unusual high lactate, in combination with an insidious onset and a patient who was relatively stable and awake, without need for mechanical ventilation. These two findings are the key clues to come to a rapid and correct diagnosis of a type B lactic acidosis. The diagnosis was confirmed in our case by measuring the blood metformin level, which was in the toxic range (see table 1), the levels of the other toxic substances were normal.

Metformin is a small molecule. It is almost exclusively (80-100%) eliminated in the urine in an unchanged form (Lalau et al., 2014). Therefore, in patients with renal failure, accumulation of metformin occurs; accordingly, the dose of metformin should be adapted to the renal function (Arnauts et al., 2014). Although the patient in our case report had a small atrophic right kidney, she had normal serum creatinine levels before the current event, highlighting that it is not absolute kidney function itself, but an (unacknowledged) rapid decrease of the kidney function that is potentially dangerous. Restrictions of metformin use solely based on renal function are thus not very useful. Lalau et al. (2014) reviewed different guidelines on the prescription of metformin, and most just provided a specific recommendations to withhold the drug altogether rather than adapt the dose according to renal function, which would be much more logical. Taking together the low incidence of MALA (Salpeter et al., 2010), the need for presence of other factors causing the metformin accumulation and development of lactic acidosis (Lalau et al., 2014)and the proven pleiotropic beneficial effects of metformin, one should consider carefully when withdrawing metformin from chronic treatment because of the fear for lactic acidosis. In addition, it should not be neglected that other therapies for diabetes mellitus such as insulin and sulfonylurea are not without adverse effects either: they significantly increase the risk for severe hypoglycemia (Bennet et al., 2011; McIntosh et al., 2011). Severe hypoglycemia is a recognised risk factor for cardiovascular events, coronary artery disease, congestive heart failure and even death (Hsu et al., 2013; Brodovicz et al., 2013; Zhao et al., 2012; Zoungas et al., 2010; McCoy et al., 2013).As reasoned by Lalau et al. (2014), there are currently strong arguments to prescribe an adjusted dose of metformin on

individual basis, taking into account the stability of the patients kidney function, presence of other comorbidities like liver disease, and concurrent medications, rather than just withholding metformin because of reduced kidney function. Our case report adds to this discussion as it demonstrates that MALA indeed can be treated successfully, when recognized on time.

Dialysis is an effective intervention to treat MALA in case of metformin accumulation, as metformin is a small, non-protein bound molecule, which is effectively removed by dialysis. Because of the large distribution volume of metformin due to intracellular penetration, there is a rebound effect of the plasma concentration observed after dialysis (Pearlman et al., 1996). Therefore, although in lack of large cohort data, prolonged or repeated renal replacement therapy is proposed as dialysis modality of choice for MALA (Keller et al., 2011). Besides elimination of metformin and lactate, early start of dialysis is important for correcting metabolic acidosis, correcting intravascular volume as well as restoring hemodynamic stability. In our case, we observed a rapid improvement of the patient after the start of dialysis.

In conclusion, when confronted with severe lactic acidosis in a relative hemodynamic stable patient, one should first exclude type B lactic acidosis as the cause of the event. MALA is a serious condition with a high mortality rate, but occurs infrequently. Mostly, it is associated with a better prognosis than lactic acidosis of another cause on condition of a timely diagnosis. Fast recognition and rapid initiation of dialysis lead to quick recovery and stabilization of our patient. Clinicians should be aware of the clinical presentation, the risk factors to develop MALA and the correct treatment. A general strategy to withdraw metformin in patients with renal insufficiency because of fear for MALA is probably no longer warranted given the many proven benefits of this molecule. The fact that MALA can also occur in patients with a previously normal renal function, and the predictability of dose-adjustment in those with reduced stable renal insufficiency should lead to a more patient-oriented decision when to stop metformin.

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