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Brief Report

Metformin-Associated Lactic Acidosis (MALA). Our experiencie and a review

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ABSTRACT

Introduction: Metformin (a biguanide) for the treatment of Type 2 Diabetes Mellitus is widely used worldwide. However, is a double-edged sword for critically ill patients. One of the most important problems with its use is the risk of developing metformin-associated lactic acidosis (MALA). We present our 10-year experience with lactic acidosis attributed to MALA as well as a review of the literature.

Material and methods: We reviewed admissions to the Intensive Care Unit (ICU) of a secondary-level hospital (630 inpatient beds) with diagnoses of "metabolic acidosis," "lactic acidosis," and "metformin-associated lactic acidosis" from January 2014 to June 2024. Data were collected from patients' electronic medical records and entered into an Excel® document for analysis.

Results: Of the total 72 cases reviewed, 11 were included. Nine cases were male (81.82%), with a mean age of 75.36 years (ages ranging from 63 to 80 years). None of the cases had a history of chronic kidney disease, but all presented with acute renal failure. Renal replacement therapies (RRT) were used in all cases, with 6 patients initially treated with and 9 patients with conventional hemodialysis. The mortality rate was 0%. However, in the literature MALA presents a mortality exceeding 10% according to several studies.

Conclusions: MALA is a very serious condition and early diagnosis is very important. The use of renal replacement therapies is of Paramount importance as well as clinical suspicion.

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Acidosis láctica asociada a metformina (ALAM): nuestra experiencia y una revisión

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RESUMEN

Introducción: La metformina (una biguanida) para el tratamiento de la diabetes mellitus tipo 2 es ampliamente utilizada en todo el mundo. Sin embargo, es un arma de doble filo para los pacientes críticos. Uno de los problemas más importantes con su uso es el riesgo de desarrollar acidosis láctica asociada a metformina (ALAM). Presentamos nuestra experiencia de 10 años con acidosis láctica atribuida a ALAM, así como una revisión de la literatura.

Material y métodos: Se revisaron los ingresos a la Unidad de Cuidados Intensivos (UCI) de un hospital de segundo nivel (630 camas de hospitalización) con diagnósticos de "acidosis metabólica", "acidosis láctica" y "acidosis láctica asociada a metformina" de enero de 2014 a junio de 2024. Los datos se recolectaron de las historias clínicas electrónicas de los pacientes y se ingresaron en un documento Excel® para su análisis.

Resultados: Del total de 72 casos revisados, se incluyeron 11. Nueve casos fueron varones (81,82%), con una edad media de 75,36 años (rango de edad de 63 a 80 años). Ninguno de los casos tenía antecedentes de enfermedad renal crónica, pero todos presentaron insuficiencia renal aguda. Se utilizaron terapias de reemplazo renal (TRR) en todos los casos, con 6 pacientes tratados inicialmente con hemodiálisis y 9 pacientes con hemodiálisis convencional. La tasa de mortalidad fue del 0%. Sin embargo, en la literature, la ALAM presenta una mortalidad superior al 10% según varios estudios.

Conclusiones: La ALAM es una enfermedad muy grave y el diagnóstico precoz es muy importante. El uso de terapias de reemplazo renal es de suma importancia, así como la sospecha clínica.

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1. INTRODUCTION

Metformin (a biguanide) for the treatment of Type 2 Diabetes Mellitus is widely used worldwide and is considered the treatment of choice [1]. Metformin is a double-edged sword for patients. On the one hand, it helps to control hyper-glycemia via inhibition of hepatic gluconeogenesis. On the other hand, during critical illness, metformin accumulation and severe toxicity in the form of metformin-associated lactic acidosis (MALA) can occur [2]. Its use is contraindicated in patients with severe acute renal failure and in situations where kidney function may be altered, such as dehydration, sepsis, or shock [3].

This contraindication is primarily due to the risk of developing MALA, a very serious and potentially fatal complication [4, 5]. It is estimated that the incidence of MALA is 4.3 cases per 100,000 patients per year, although it could be higher as it is underdiagnosed since it can mimic other conditions such as sepsis or intestinal ischemia [6]. The risk factors for the development of MALA include chronic kidney disease, heart failure, alcohol consumption, liver disease, and shock [7, 8]. MALA incidence drops when the contraindications and correct rules of prescription are respected, such as hypoxic conditions, impaired lactate clearance, and impaired metformin clearance [9].

The mortality, without treatment, of MALA is very high. That is why it is very important to know and suspect this entity to establish early treatment [4].

We present our 10-year experience with lactic acidosis attributed to metformin (MALA) as well as a review of the literature.

2. MATERIAL AND METHODS

We reviewed admissions to the Intensive Care Unit (ICU) of a secondary-level hospital (630 inpatient beds) with diagnoses of "metabolic acidosis," "lactic acidosis," and "metformin-associated lactic acidosis" from January 2014 to June 2024. Patients under 18 years old were excluded. 72 cases were collected. Of these, 61 patients were excluded due to diagnoses other than MALA (mostly diabetic ketoacidosis). Patients who were taking metformin and presented with lactic acidosis without an alternative diagnosis were included in the review.

Table 1: Patients characteristics affected by metformin-associated lactic acidosis

N	Sex	Age	Surg.	Inf	GI	AKI	MV	NE	CD	CRR	pH arrival	Lactate arrival (mg/dL)	Max lactate (mg/dL)	Metf. level (mcg/mL)	D
1	M	78	N	N	Y	Y	Y	Y	Y	N	6.96	49	75	13.88	N
2	M	63	N	N	N	Y	Y	Y	Y	Y	6.9	159	170	-	N
3	M	78	Y	N	N	Y	Y	Y	Y	Y	7.1	126	135	34.29	N
4	M	74	Y	Y	Y	Y	N	Y	N	Y	7.05	153	156	31	N
5	F	80	N	N	Y	Y	N	Y	Y	N	7.1	153	153	-	N
6	M	78	N	N	Y	Y	N	Y	Y	N	6.9	85	107	-	N
7	M	71	N	N	Y	Y	N	Y	N	Y	7.15	59	59	-	N
8	M	73	N	N	Y	Y	Y	Y	Y	Y	6.8	162	180	-	N
9	M	76	N	N	Y	Y	N	N	Y	N	7.1	101	101	-	N
10	M	78	N	N	Y	Y	Y	Y	Y	N	6.9	85	111	-	N
11	F	80	N	N	Y	Y	N	N	Y	N	6.92	63	63	-	N

M: Male; F: Female; Surg: Previous surgery; Inf: Infection; GI: Diarrhoea/vomiting; AKI: Acute Kidney injury; MV: Mechanical ventilation; NE: Norepinephrine; CD: Convectional dialysis; CRR: Continuous renal replacement; Metf: Metformin; D: Death.

From these cases, we gathered data via the electronic medical record system, including sex, age, ICU and hospital stay duration, personal history, presence of infection or prior surgery, development of acute renal failure, need for orotracheal intubation, vasopressor drugs, conventional dialysis (and the number of sessions) or continuous veno-venous hemodialysis, and analytical values (blood pH, lactic acid levels, blood potassium, and metformin levels). Renal recovery in patients with acute kidney injury (AKI) and survival were reviewed as outcome measures.

We collected data from patients' electronic medical records and entered into an Excel® document for analysis. We use Mean for continuous variables.

3. RESULTS

Of the total 72 cases reviewed, 11 were included. Nine cases were male (81.82%), with a mean age of 75.36 years (ages ranging from 63 to 80 years). None of the cases had a history of chronic kidney disease, but all presented with acute renal failure upon admission to the ICU. Diarrhea and/or vomiting were present in 81.82% of cases, and two had undergone recent surgery. Upon arrival at the hospital, they presented with a blood pH of 6.9 and an average lactic acid level of 108.6 mg/dL (normal <20 mg/dL) with a range between 49-153 mg/dL. In 10 patients (90.91%), norepinephrine infusion was necessary to maintain blood pressure.

Renal replacement therapies (RRT) were used in all cases, with 6 patients initially treated with CVVHD (between 24 and 96 hours) and 9 patients with conventional hemodialysis (either as the first option or following CVVHD), with a total of 1 to 4 sessions. No patients died, and one patient developed chronic renal failure without requiring hemodialysis. Blood metformin levels were measured in 3 patients, with levels of 13.88, 31, and 34.29 mcg/mL (toxic levels start at 5 mcg/mL).

The collected data are shown in Table 1.

4. DISCUSSION

Metformin is a widely used hypoglycemic drug worldwide for the treatment of Type 2 Diabetes Mellitus. However, it is important to consider the development of metformin-associated lactic acidosis (MALA), a potentially fatal condition [4].

Lactate is produced through glycolysis in the liver, intestines, and peripheral tissues, and its clearance occurs mainly in the liver and kidneys[7]. Lactic acidosis is classified as Type A when caused by hypoxia and Type B when the trigger is non-hypoxic, as in the case of MALA [8].

Metformin is absorbed in the duodenum-jejunum (40%) and in the ileum-colon (10%), circulates freely in plasma, and is eliminated via the kidneys [3, 8]. In cases of renal dysfunction, the drug accumulates in the body, potentially causing lactic acidosis through complex molecular mechanisms that increase the cytoplasmic lactate/pyruvate ratio, resulting in mitochondrial dysfunction and elevated lactic acid [9].

Risk factors for MALA development include chronic kidney disease, heart failure, alcohol consumption, liver disease, and shock [7, 8].

According to a population-based study conducted in the United Kingdom, metformin use, compared to no metformin use, has been associated with about 4.5-fold greater incidence of lactic acidosis in patients with type 2 diabetes

mellitus (45.7 versus 11.8 cases per 100000 patient-years), with increasing risk with worsening kidney function [10].

None of our patients had a prior history of chronic kidney disease, but all developed severe acute renal failure, likely due to hypovolemia from gastroenteritis and sepsis (most patients had nausea and vomiting). These findings are similar to those reported in other studies [4, 11].

The diagnosis is based on clinical presentation after ruling out other possible causes of severe lactic acidosis (such as sepsis and intestinal ischemia). Measurement of plasma metformin levels is possible, but it is important to note that it is not always available and that it takes time, which is often unavailable due to the severity of the case. Therefore, treatment should be initiated as soon as MALA is suspected. In our series, elevated plasma metformin levels were confirmed in three patients. In the remaining cases, levels were not requested due to the lack of availability.

Treatment is based on supportive measures for shock, including fluid therapy, vasopressors, mechanical ventilation, and primarily renal replacement therapy (RRT) [5, 8, 9]. Metformin is a small molecule with low protein binding, making it dialyzable [11].

There are no clearly established criteria for initiating RRT in MALA patients [11, 12], but it is indicated in the presence of severe metabolic acidosis with pH<7.1, lactate >20 mmol/L, shock, or altered consciousness. However, even in the absence of these criteria, RRT should be considered in suspected MALA due to the potential severity and the good response to dialysis [4, 8, 11].

In our series, all patients received renal replacement therapy, and the mortality rate was 0%. In other series, mortality rates range from 30-50% [13]. The choice of RRT modality depends on the patient's stability, availability, and tolerance. The duration of therapy varies depending on the series, and consideration should be given to analytical values and the patient's clinical condition (in cases of acute renal failure, the half-life of metformin increases from 4.9 hours to 52 hours) [4, 8, 12]. Taking into a count that is an underdiagnosed entity [4] and the high mortality reported in the literature [13] makes knowledge of this entity very important in order to establish adequate treatment.

In our opinion, supportive measures and RRT should be initiated as early as possible in suspected MALA, as it is a condition with high mortality that can respond well to treatment. We also believe that MALA is underdiagnosed, as it can be mistaken for conditions such as sepsis, and therefore, plasma metformin levels should be requested in patients with suspected MALA.

5. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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