Case report

Metformin-related lactic acidosis: Case report

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ABSTRACT

Lactic acidosis is defined as the presence of pH <7.35, blood lactate >2.0 mmol/L and PaCO2 <42 mmHg. However, the definition of severe lactic acidosis is controversial. The primary cause of severe lactic acidosis is shock. Although rare, metformin-related lactic acidosis is associated with a mortality as high as 50%. The treatment for metabolic acidosis, including lactic acidosis, may be specific or general, using sodium bicarbonate, trihydroxymethanamine, carbicarb or continuous haemodiafiltration. The successful treatment of lactic acidosis depends on the control of the aetiological source. Intermittent or continuous renal replacement therapy is perfectly justified, shock being the argument for deciding which modality to use. We report a case of a male patient presenting with metformin poisoning as a result of attempted suicide, who developed lactic acidosis and multiple organ failure. The critical success factor was treatment with continuous haemodiafiltration.

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Acidosis láctica por metformina: reporte de caso

RESUMEN

Definimos acidosis láctica en presencia de pH <7.35, lactato en sangre >2.0 mmol/L y PaCO2 <42 mmHg. Por otro lado, la definición de acidosis láctica grave es controvertida. La causa principal de acidosis láctica grave es el estado de choque. La acidosis láctica por metformina...
**Introduction**

La acidosis láctica es definida como la presencia de pH <7.35, lactato >2.0 mmol/L y PaCO₂ <42 mmHg. No obstante, la definición de acidosis láctica severa es controvertida. Muchos médicos asocian la severidad de la acidosis láctica con pH <7.2 o con efectos deletéreos, principalmente hemodinámicos, requiriendo tratamiento inmediato.7-9 La principal causa de acidosis láctica se asocia con una mortalidad de hasta 50% si se produce adecuado tratamiento etiológico, y 100% cuando el pH se mantiene <7.0.5

Sin embargo, una causa menos común de acidosis láctica es la intoxicación metformínica, con una mortalidad de hasta 50%. La incidencia es de 3 casos cada año por cada 100,000 pacientes tratados en el hospital. El principal riesgo para el desarrollo de acidosis láctica después de la ingesta de metformina es el deterioro renal presente en diabéticos. El riesgo es mayor en aquellos que presentan intencionalmente intoxicación con metformina, como cuando se desarrolla acidosis láctica y el paciente vuelve a probarse autoinoculación para causar el estado de choque. Presentamos el informe de un caso de un paciente masculino con intoxicación por metformina como intento suicida, quien desarrolló acidosis láctica y multigénesis múltiple en cuya base para el éxito del caso fue el tratamiento con hemodiálisis continua.

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**Table 1 - Biochemical and haemodynamic variables for hospital admission.**

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Haemodynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.0</td>
</tr>
<tr>
<td>Lactate</td>
<td>&gt;15 mmol/L</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>9.4 mEq/L</td>
</tr>
<tr>
<td>Urea</td>
<td>72.8 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.9 mg/dL</td>
</tr>
<tr>
<td>Potassium</td>
<td>6.4 mEq/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>60 mg/dL</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>90/50 mmHg</td>
</tr>
<tr>
<td>Heart rate</td>
<td>50 lpm</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.4 mcg/kg/min</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.2 mcg/kg/min</td>
</tr>
<tr>
<td>CI</td>
<td>2.8 l/min/m² BS</td>
</tr>
</tbody>
</table>

**Clinical case**

Presentamos el caso de un paciente de 74 años de edad, masculino, procedente de Veracruz, México, con una historia de diabetes mellitus tipo 2 diagnosticada 26 años antes, tratado con metformina 850 mg/día y glibenclamide 10 mg/día, a diálisis con schizofrenia tipo psicótico de manera irregular con olanzapina, y no otro relevante historial. Siguiendo el intencional consumo de 20 tabletas de metformina, el paciente desarrolló un cuadro clínico caracterizado por náusea, vomito y deshidratación, con pérdida de conciencia que prometió transferencia para tratamiento.

Al llegar al departamento de emergencia, el paciente fue establecido en ventilación mecánica invasiva (IMV) debido a su condición neurológica, y se requirió el uso de vasoconstrictores debido a la inestabilidad hemodinámica con ritmo nodal-cardiac.

La historia clínica inicial reveló acidosis láctica, hiperglicemia, hipercaliemia, edema pulmonar, disnea, diarrea y vomito. Se inicio tratamiento con metformina, con el aporte de bicarbonato de sodio, dextrosa, bicarbonato de sodio y el uso de vasoconstrictores.

Al día siguiente, se inició tratamiento con metformina, con el aporte de bicarbonato de sodio, dextrosa, bicarbonato de sodio y el uso de vasoconstrictores.

**Pathophysiology of metformin-related lactic acidosis**

Metformina es un biguanida y el primer fármaco de elección para control de azúcar en pacientes con DM tipo 2 debido a su metabolismo y beneficios cardiovasculares.87 El efecto adverso más comúnmente asociado con su uso gastrointestinal, incluyendo náusea, vomito y diarrea. Sin embargo, el efecto adverso más temido es la acidosis láctica.79 Pyruvate-derived lactate is the end product of glycolysis in anaerobic conditions. Humans produce 1500 mmol of lactate per day (0.8 mmol/kg/h) in
Traditionally, whereby reduced brain pH: 7.32, 7.31, 7.47. Recently, in the context of the Krebs cycle, it has been postulated that in order for lactic acid to occur, the hydrogen ions (H+) required for conversion had to be produced through adenosine triphosphate (ATP) hydrolysis not used in the cytoplasm.

Any imbalance in the form of increased lactate production, reduced clearance, or both, will give rise to serum lactate elevation (normal <2 mmol/L). As a molecule, lactate is found in anion form and not as lactic acid. In the past, it was postulated that in order for lactic acid to occur, the hydrogen ions (H+) required for conversion had to be produced through adenosine triphosphate (ATP) hydrolysis not used in the cytoplasm.

Recently, an explanation for the development of acidosis has been postulated on the basis of Stewart’s physicochemical theory, according to which pH changes depend on the partial pressure of carbon dioxide (pCO2), the total concentration of non-volatile weak acids, and the strong ion difference (SID), the latter being the cation-anion difference in the extracellular fluid (Na+ + K+ + Mg2+ + Ca2+)−(Cl− + Lactate−). This means that an increase in lactate will reduce the SID and, in turn, pH, creating or perpetuating lactic acidosis. Traditionally and in accordance with Cohen’s classification, lactic acidosis is divided into hypoaemic type A and non-hypoaemic type B (Table 3).

It has been considered that the mechanism for the production of lactic acidosis is multi-factorial: genetic, metabolic oxidation suppression, and Krebs cycle enzyme suppression. However, the most widely accepted mechanism is the one proposed by Owen, whereby metformin affects electron transport, increasing the concentration of reduced nicotinamide adenine dinucleotide or NADH and inhibits metabolic oxidation, inducing anaerobic metabolism. Understanding the process of cell respiration is important in order to understand the mechanism through which metformin poisoning causes lactic acidosis type B2. ATP is the “cell's top energy currency”, indispensable for physiological cell function. A process known as cell respiration is required in order to obtain this energy currency in aerobic metabolism.

| Table 2 – Behaviour of the biochemical variables of the patient during slow CRRT and on discharge from the ICU. |
|------------------|----------------|----------------|
| Variable         | 24 h           | 48 h           | 72 h           |
| pH               | 7.32           | 7.31           | 7.47           |
| HCO3− (mEq/L)    | 20.1           | 20.6           | 22.6           |
| Lactate (mmol/L) | 7.8            | 4.5            | 1.8            |
| pCO2 (mmHg)      | 39             | 41             | 31             |
| Base (mmol/L)    | −6.0           | −5.7           | −1.1           |
| pO2 (mmHg)       | 111            | 109            | 165            |
| PT (s)           | 21             | 19             | 17.4           |
| PTT (s)          | 56             | 33.2           | 31.9           |
| Glucose (mg/dl)  | 108            | 160            | 94             |
| Urea (mg/dl)     | 74.9           | 59.9           | 42.8           |
| Creatinine (mg/dl)| 2.1           | 1.6            | 1.2            |
| Na+ (mEq/L)      | 145            | 140            | 136            |
| K+ (mEq/L)       | 3.8            | 4.0            | 3.6            |
| Cl− (mEq/L)      | 104            | 103            | 101            |

pH: negative log of hydrogen ion concentrations; HCO3−: bicarbonate; pCO2: partial pressure of carbon dioxide; pO2: partial pressure of oxygen; PT: prothrombin time; PTT: partial thromboplastin time; Na+: sodium; K+: potassium; Cl−: chlorine.

Source: Authors.

| Table 3 – Aetiologic classification of metabolic acidosis. |
|------------------|----------------|
| Classification   | Causes                              |
| Type A           | Tissue hypoperfusion                 |
| B1               | SIRS, asthma, liver failure          |
| B2               | Metformin, paracetamol, alcohols     |
| B3               | Inborn errors of metabolism         |

HIV: human immunodeficiency virus; SIRS: systemic inflammatory response syndrome; CO: carbon monoxide; PN: parenteral nutrition. Source: Authors.

Cell respiration is defined as the generation of energy from nutrient oxidation and it consists of three stages: glycolysis, citric acid cycle (Krebs cycle) and oxidative phosphorylation. Glycolysis consists of a set of enzymatic reactions designed to convert glucose into two pyruvate molecules with energy production (2ATP + 2NADH + 2FADH2). In the glycolysis and Krebs cycle pathways, energy carriers (NADH+ and FADH2) are derived so that they can be used in oxidative phosphorylation through mitochondrial complexes which play the role of electron mobilisers. This process stops when NADH+ oxidises to NAD+ and gives 2 electrons to complex I; these electrons are transported between complexes II, III, IV and arrive at the mitochondrial matrix in order to bind to an oxygen moiety and 2H+ to form water. Every time electrons travel across complexes, they pump H+ towards the mitochondrial intermembrane space, creating a proton gradient in complexes I (4H+), III (4H+), IV (2H+) and IV (2H+); this gradient is again transported towards the mitochondrial matrix through the ATP synthase complex in order to phosphorylate ADP and produce 4 ATP molecules, resulting in 38 ATPs during the entire cell respiration (2 ATPs are used as currency to initiate glycolysis). In short, the purpose of the three stages of cell respiration is to generate the necessary energy to maintain optimal cell metabolism. When some, for some reason, the aerobic pathway is not followed, the anaerobic pathway will be activated in order to produce energy. In cases of metformin overdosing, the drug binds to the mitochondrial membranes, specifically complex I, inhibiting the electron transport system (oxidative phosphorylation). When NADH is not oxidised, it accumulates, there is a change in the anaerobic mechanism with increased production of lactate, in an attempt to produce...
the necessary energy to maintain the physiological conditions of the cell. However, the level of energy is lower and only 4 ATP molecules are produced. Blood lactate accumulates, the SID is altered, and lactic acidosis ensues.

**Discussion**

Metformin is a small 165 Da molecule with an oral availability of 55% and a distribution volume of 1–5 L/kg. It is eliminated practically unchanged through the kidneys, and its total body clearance in subjects with healthy renal function is 500 ml/min, 200 ml/min with intermittent dialysis, and 50 ml/min in patients on slow continuous renal replacement therapy (CRRT). Therapeutic concentrations are 1.5–3.0 mg/L. The elimination half-life is 8–20 h in individuals with normal renal function.

Outcomes will improve when risk factors for the development of lactic acidosis are recognised, including deterioration of kidney or liver function, alcoholism, reduced tissue perfusion due to infection, age over 60 years, and heart failure in patients receiving metformin-based treatment; also, early diagnosis and timely initiation of renal replacement therapy are critical for success. The vast majority of patients admitted to the ICU with metformin-related lactic acidosis are over 65 years of age and present with haemodynamic instability and acute renal injury. Intermittent or continuous renal replacement therapy with haemofiltration to eliminate metformin and lactate from the blood is recommended, the argument being the correlation between reduction of metformin plasma levels and improvement in lactic acidosis. Hypotension is treated initially with intravenous fluids, followed by the use of vaspressors if needed. For patients with metformin poisoning, extracorporeal haemodialysis is the preferred treatment as long as there is haemodynamic stability. Although there is limited evidence regarding slow CRRT, it is preferred in patients with haemodynamic instability because it is better tolerated than haemodialysis.

The working group on extracorporeal treatments in poisoning (EXTRIP), comprised by international experts who represent different societies and specialties, makes recommendations in this regard. Extracorporeal treatment is recommended in severe metformin poisoning (1D), primarily if lactate is ≥15 mmol/L, pH ≤7.0 and standard therapy (including NaHCO₃⁻) has failed (1D), or in the presence of shock (use of vasopressors) or decline in kidney function (1D). Discontinuation of extracorporeal treatment is indicated when lactate levels are lower than 3 mmol/L and pH is higher than 7.35 (1D). Intermittent haemodialysis will always be the first option (1D), although slow CRRT will be the preferred choice in presence of haemodynamic instability (1D). Compared to lactic acidosis of a different origin, metformin-related lactic acidosis is associated with lower mortality (50% vs 74%) and has a better prognosis, even when pH is under 7.0.

On the other hand, treatment of any alteration in acid–base balance must be targeted to the underlying cause. Acidosis has a protective effect in anoxic or ischaemic cells, but that protection will be lost at a certain point, which is still a subject of controversy (pH under 7.2, HCO₃⁻ less than 10 mEq or base deficit greater than −10 mmol/L). Addressing acidosis could result in a paradoxical effect (“harm and no benefit”). Acidosis protection could be related to an enzyme “sparing” effect. Treatment of metabolic acidosis should be aimed at avoiding cell dysfunction occurring as a result of intracellular increase of Na⁺ and Ca²⁺ levels, driven by intra and extracellular pH alterations.
Take into account the Base Deficit (BD) measured at 15 min (basal) after the challenge with NaHCO3. If DB increases less than -5 at 60 min with regard to the basal, acidosis is secondary to hipoperfusion. If DB is > -5 to -10 regarding the basal at 60 min, consider acids exogenous production.

**LACTIC ACIDOSIS**
Lactate >2.0 mmol/L, pH <7.35, PaCO2 <42 mmHg

**CHALLENGE** with a BOLUS of NaHCO3 mEq:
(Base deficit x 0.2 x Predicted weight in Kg)

**HYPOPERFUSION**
**BASE DEFICIT CHANGES:**
<-6 mmol/L FROM BASELINE AT 60 MINUTES

**BASE DEFICIT CHANGES:**
>-5 to -10 mmol/L FROM BASELINE AT 60 MINUTES

**EXOGENOUS PRODUCTION**

**ΔCO2/ΔavO2**
> 1
< 1

**OPTIMISE HAEMODYNAMICS**

**FLUID CHALLENGE:**
30 ml/kg
0.9% SALINE SOLUTION

**MAP**
< 65 mmHg

**INITIATE VASOPRESSOR**

**RENAL REPLACEMENT THERAPY**

**MAP**
> 65 mmHg

**MAP**
> 6 mmHg

**> 6 % %**

**< 6 mmHg**

**< 60 %**

**INITIATE INOTROPE**

**TREAT UNDERLYING CAUSE**

**CONSIDER TREATMENT WITH NaHCO3:**
- pH < 7.20
- Added cardiovascular disease
- Arrhythmias
- Haemodynamic instability

**CONSIDER TREATMENT WITH RRT:**
- pH < 7.20 ≥ 15 mmol/L
- Lactate is ≥ 4 horas
- Vasopressor use

**OPTIMISE:**
- SpO2 ≥ 92%
- Hb ≥ 7.0 g/dL o ≥ 10 g/dL en ischemic heart disease
- VO2 normal?
- CVP >8 y < 12 cmH2O

**NON-HAEMODYNAMIC CAUSES**

**ΔCO2**
*

**SvcO2**
*

**Fig. 2 – Algorithm for the diagnosis and treatment of lactic acidosis.**
NaHCO3: sodium bicarbonate; pH: negative log of hydrogen ion concentrations; PaCO2: carbon dioxide arterial pressure; ΔCO2: carbon dioxide difference; ΔCO2/ΔavO2: carbon dioxide difference between arterio-venous oxygen difference; MAP: mean arterial pressure; SvcO2: central venous oxygen saturation; SpO2: peripheral oxygen saturation; Hb: haemoglobin; VO2: oxygen consumption; CVP: central venous pressure; RRT: renal replacement therapy.

Source: Author.
The use of sodium bicarbonate (NaHCO$_3$) is a controversial strategy that has not been fully validated in the clinical scenario of lactic acidosis and haemodynamic instability, regardless of the aetiology. This measure is considered a bridging therapy while waiting for aetiologic treatment. Even the international guidelines of the Surviving Sepsis campaign recommend the use of NaHCO$_3$ when pH is less than or equal to 7.15 in order to improve the haemodynamic state or reduce the number of vasopressors in patients with hypoperfusion-induced lactic acidosis.$^{37}$ A recent publication of a review study that evaluated the use of NaHCO$_3$ in the treatment of lactic acidosis due to sepsis reported that the routine use of NaHCO$_3$ continues to be controversial, and concluded that further studies are required in order to determine a potential benefit.$^{38}$ NaHCO$_3$ administration may give rise to side effects, including increased production of carbon dioxide(CO$_2$) and reduced ionised calcium, which may contribute to diminished right ventricular contractility or vascular tone. Moreover, there is the potential for a paradoxical effect because of the improvement in extracellular pH but not so of the intracellular pH (intracellular hypercapnia).$^{39}$

The use of NaHCO$_3$ in the treatment of metabolic acidosis has been shown to have beneficial effects in diseases where there is evidence of HCO$_3$ loss. In contrast, no benefit has been observed when it has been used to address metabolic acidosis from other causes.$^{40}$ Additionally, the use of NaHCO$_3$ has been proposed as a diagnostic method in the form of a bicarbonate challenge to determine the origin of metabolic acidosis, mainly in patients with septic shock and severe metabolic acidosis and high risk of hypoperfusion-associated complications such as hypoxic hepatitis, a condition that usually occurs after prolonged hypoperfusion, as well as inflammation, hypoxaemia and hypoxia. It would be wise to assume that prompt and accurate diagnosis of metabolic acidosis (hypoperfusion) will lead to early targeted treatment or help consider a different source (exogenous acid production) at an earlier stage, in order to modify the diagnostic and therapeutic approach.$^{41}$

We present the management algorithm used in our critical care unit in cases of lactic acidosis (Fig. 2).

**Conclusion**

Lactic acidosis is common in critically ill patients and correlates with severity and prognosis. However, the aetiology of lactic acidosis is a key determining factor for outcome. Timely diagnosis of the mechanism and cause of lactic acidosis will favour early targeted treatment. Treatment success depends on the control of the aetiologic source. Metformin-related lactic acidosis has a better prognosis lactic acidosis induced by septic shock. Intermittent or continuous renal replacement therapy should be used as the first step in the treatment of metformin-related lactic acidosis.

**Ethical disclosures**

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

**Confidentiality of data.** The authors declare that no patient data appears in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appears in this article.

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**Conflict of interest**

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**References**