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CLINICAL CASE
Bilingual edition English/Spanish

Toxicity induce by chlorine dioxide

Intoxicación por dióxido de cloro

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Introduction

Chlorine dioxide is a highly water soluble gaseous chemical compound used in a wide variety of applications as an industrial bleaching agent, a surface disinfectant and a water purifier given its antimicrobial properties[1].

During the COVID-19 pandemic, the oral use of chlorine dioxide solutions was touted through the social media and different websites as a way to treat or prevent SARS-CoV-2 infection. The Spanish Agency for Medicines and Medical Devices as well as other countries' healthcare agencies have issued alerts warning the public about the potential gastrointestinal, hematologic and renal risk of such solutions, which in some cases may require users to be hospitalized[2].

This report describes a case of acute hepatotoxicity, low blood pressure and disseminated intravascular coagulation (DIC) associated with chlorine dioxide poisoning.

Description of the case

This was a 67-year-old non-alcoholic male patient without any relevant medical history or regular use of medication. Having developed low-grade fever and myalgia, he self-administered 3-4 drops of chlorine dioxide 25%, which he acquired online, every 8 hours for 7-8 days. He subsequently presented to the emergency department with signs of asthenia, nausea and vomiting, dehydration, weight loss, dysuria and choluria. The patient was without fever with blood pressure of 102/59 mmHg. The physical examination revealed a poor general condition with marked mucocutaneous pallor. No significant alterations were observed at neurologic, respiratory, cardiac or abdominal level or in the patient's limbs. Table 1 shows the most noteworthy analytical alterations observed. Oxygen saturation at ambient air was 97%, while the methemoglobin (MHb) fraction was 0.8% in arterial blood. The peripheral blood smear obtained did not present with immature forms or any significant alterations of erythrocyte morphology, except for a few isolated echinocytes and codocytes, which were visible although the quality of the sample was not optimal. The urine sediment revealed hemoglobinuria and the presence of erythrocytes (48 cells/µL). A nasopharyngeal study of the influenza A and B viruses and of SARS-CoV-2 was negative. A chest x-ray and an abdominal ultrasonography were performed, which did not show any significant alterations. Antibiotic cover was prescribed with imipenem/cilastatin as well as intensive fluid replacement therapy and pooled platelet transfusion. Given the persistence of low blood pressure (80/40 mmHg) in spite of intensive rehydration, a decision was made to transfer the patient to the intensive care unit (ICU), where an infusion of noradrenaline was performed. Acute infectious hepatitis A, B and C as well as HIV were ruled out by a test panel; and autoimmune diseases, Wilson's disease and alpha-1-antitripsin deficit were ruled out by antinuclear, antimitochondrial, smooth muscle, anti-LKM and anticytoplasmatic antibody tests. After 24 hours in the ICU, the patient's hemodynamic condition stabilized and he was transferred to a general ward, where his hepatic and hematologic parameters experienced a gradual improvement (Table 1), without requiring any additional treatment. Urine and blood cultures negativized

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Chlorine dioxide; Sodium chlorite; Hepatotoxicity; Disseminated intravascular coagulation; COVID-19.

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on day 6. The patient was discharged at 8 days from admission, being warned about the risks of using chlorine dioxide as a therapeutic agent.

Discussion

Upon reduction, chlorine dioxide releases highly reactive chlorite ions with high oxidative potential, which can inflict damage to the cells that are exposed to it[1]. The corrosion and irritation of the digestive mucosa caused by chlorine was what brought on the patient's initial gastrointestinal symptoms. In an analysis of 53 cases of chlorine dioxide-induced poisoning, the main symptoms reported were nausea, vomiting, abdominal pain and diarrhea[3]. The digestive discomfort experienced by our patient could also have been associated with acute hepatitis. Chlorine dioxide-induced poisoning is not usually accompanied by hepatic symptoms. The US Food and Drug Administration Pharmacovigilance System reported the case of a chlorine dioxide-induced hepatobiliary alteration in a 6-year-old girl[4]. Our patient presented with a cholestatic pattern of hepatotoxicity with elevated cytolytic markers.

A usual hematological complication derived from chlorite ion poisoning is intravascular hemolysis, which results from an increase in the stiffness (and subsequent rupture) of red blood cell membranes[1,5-8]. The poisoning episode suggests that our patient's anemia was of a hemolytic nature, although no irregular forms were observed in the peripheral blood smear and no hemolytic parameters (such as hemolysis or reticulocyte count) were observed.

Another typical hematologic alteration is the formation of MHb as a result of la oxidation of the iron atom in the heme group in hemoglobin. The severity of MHb is related with how much of the toxic substance is ingested. Contrary to other cases reported in the literature[1,5,6,8,9], our patient did not develop MHb, probable due to the moderate amount of chlorine dioxide ingested. Given its anti-oxidant properties, methylene blue is the antidote of choice for MHb as it boosts the activity of NADH-MHb-reductase. Nevertheless, its use in contraindicated in patients with a deficit of glucose-6-phosphate dehydrogenase. The efficacy of methylene blue in patients with chlorine dioxide poisoning is debatable. In our patient, use of the antidote following the onset of hemolysis did not prove effective, while its administration in the early phases of the poisoning episode (first 4-6 hours) showed itself beneficial[1,6,9].

DIC is a condition characterized by a systemic activation of coagulation resulting from intravascular hemolysis in cases of chlorite derivative-induced toxicity[1,5,8,9]. Our patient developed DIC manifested by thrombocytopenia, increased production of fibrinolytic enzymes and altered coagulation times. Clinically, no hemorrhagic or thrombotic complications were observed, although transfusion of platelet concentrate was required.

As regards treatment, replacement renal therapy has been used in cases of severe poisoning with renal involvement. Continuous renal replacement techniques proved more effective in patients with hemodynamic instability[8-10].

In short, the COVID-19 pandemic gave rise to an increased offering of chlorine dioxide-derived therapies, although such treatments lack official approval and are not backed by scientific evidence. As illustrated by our case, consumption of chlorine dioxide may result in dire health consequences. In this context, correct dissemination of health warnings to the public is of particular importance.

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Conflict of interests

The authors declare no conflict of interest.

Table 1. Evolution of the hematologic, hepatic and biomechanical analytical parameters of the studied patient on admission

Parameter/unit/reference value	Day 0*	Day +1**	Day +8***	Day +63****
Hemoglobin, g/dL (13-18)	**9.7**	**9.2**	**10.4**	13.2
Platelets x 10⁹/L (130-450)	**24.0**	**53.0**	377.0	390.0
Leukocytes x 10⁹/L (4.0-11.5)	**20.93**	**18.0**	11.10	5,002.00
aPTT ratio (0.85-1.30)	**0.76**	**0.79**	0.85	0.85
PT ratio (0.85-1.20)	**1.30**	**1.30**	1.04	1.04
INR (–)	**1.29**	**1.29**	–	–
Fibrinogen, mg/dL (170-470)	**593**	**599**	–	356
D-dimer, FEU (–)	**3,780**	**3,890**	–	299
Creatinine, mg/dL (0.72-1.18)	1.04	0.90	**0.65**	1.01
Sodium, mEq/L (135-145)	**129**	**133**	**134**	138
Potassium, mEq/L (3.5-5.0)	**3.3**	3.6	**5.1**	4.1
Calcium, mg/dL (8.5-10.1)	**8.1**	**8.1**	**8.3**	8.7
Chlorine, mEq/L (–)	**108**	**99**	–	88
Total bilirubin, mg/dL (0.2-1.0)	**13.20**	**11.50**	**3.28**	0.90
Direct bilirubin, mg/dL (0.0-0.3)	**–**	–	**2.5**	0.2
AST, UI/L (5-40)	**178**	**159**	**70**	36
ALT, UI/L (16-53)	**129**	**119**	**117**	45
AF, U/L (46-116)	**145**	**130**	**123**	69
Albumin, g/dL (3.5-5.0)	**2.8**	–	**3.2**	3.8
Total proteins, g/dL (6-8)	**5.1**	–	–	6.1
GGT, U/L (7-61)	**78**	**65**	**64**	55
LDH, UI/L (120-246)	**292**	–	205	129
CRP, mg/dL (0-1)	**15.26**	**13.90**	–	**1.90**
Amylase, U/L (28-100)	**481**	–	–	98

*Patients presents to the Emergency Area. **Admission to Intensive Care Unit. ***Last day of hospitalization. ****Outpatient setting.
AF: alkaline phosphatase; ALT: alanine aminotransferase; aPTT: activated total partial thromboplastin time; AST: aspartate aminotransferase; CRP: C-reactive protein; FEU: fibrinogen equivalent unit; GGT: gamma-glutamyl transferase; INR: international normalized ratio; LDH: lactate dehydrogenase; TP: thromboplastin time.

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