

Sodium fluoroacetate poisoning

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Abstract

Introduction: Sodium fluoroacetate, known as compound 1080, was discovered in Germany during the Second World War. It is usually used as a rodenticide, it is an odorless and tasteless substance, with a lethal dose in humans of 2 mg / kg that is why it was withdrawn from the market in some countries, including Colombia; however, it is obtained illegally. This substance has biochemical and physiological effects at the cellular level that alter the transport of citrate at the mitochondrial level, generating accumulation of lactic acid and alteration of the glucose use. The clinical manifestations are nonspecific since there is no any cardinal symptom. Therefore, its diagnosis is made due to high clinical suspicion associated with establishment of exposure to the compound in view of the difficulty to obtain paraclinical confirmation in a timely manner.

Methods: We present a case report of intentional ingestion of sodium fluoroacetate in an adolescent that is associated with an infection added to the bloodstream by methicillin- sensitive *Staphylococcus aureus* (MSSA). The patient developed multiple complications that lead to support in the Intensive Care Unit (ICU) with a satisfactory outcome. In view of the lack of a specific antidote, she was treated with ethanol in order to increase the level of acetate; thus, offering an alternative substrate to the Krebs cycle. It is suggested that the ethanol offers benefits in the acute treatment of these patients.

Results: The patient with sodium fluoroacetate poisoning and kidney failure received renal replacement therapy with a favorable evolution and survival at discharge from the intensive care unit of a third-level hospital in the city of Pereira, Risaralda, Colombia.

Conclusions: Sodium fluoroacetate poisoning is relatively rare and can cause acute kidney injury and multi-organ failure with a high rate of complications and death. A case of self-inflicted poisoning that received a timely manner continuous renal replacement therapy with a favorable outcome in terms of ICU survival was presented.

Keywords: Poisons, Blood Poisoning, Toxicology, Sodium Fluoroacetate, acute renal failure.

Intoxicación por fluoroacetato de Sodio

Resumen

Introducción: El fluoroacetato de sodio –conocido como compuesto 1080–, fue descubierto en Alemania durante la segunda guerra mundial, suele ser utilizado como raticida y se caracteriza por ser una sustancia inodora e insabora. En humanos, una dosis de 2 a mg/kg es letal; debido a su toxicidad fue retirado del mercado en algunos países, incluyendo Colombia, no obstante, se consigue de forma ilegal. Esta sustancia tiene efectos bioquímicos y fisiológicos a nivel celular que altera el transporte del citrato a nivel mitocondrial, generando acumulación de ácido láctico y alteración en la utilización de la glucosa. Las manifestaciones clínicas son inespecíficas y no existe un síntoma cardinal. Por ende, su diagnóstico se realiza por alta sospecha clínica, asociado al establecimiento de la exposición al compuesto, ya que la confirmación paraclínica es difícil de realizar oportunamente.

Métodos: Se presenta un reporte de caso de ingestión intencional en un adolescente, asociado con infección agregada al torrente sanguíneo por *Estafilococos Aureos Meticilino Sensible* (EAMS). El paciente desarrolló múltiples complicaciones y requirió asistencia en Unidad de Cuidados Intensivos (UCI) con desenlace satisfactorio. Ya que no se cuenta con antídoto específico, se le dio tratamiento con etanol para aumentar el nivel de acetato, ofreciendo así un sustrato alternativo al ciclo de Krebs. Se estima que el etanol puede ofrecer beneficios en el tratamiento agudo de estos pacientes.

Resultados: Paciente con intoxicación por fluoroacetato de sodio e insuficiencia renal, recibe terapia de reemplazo renal con un evolución favorable y supervivencia al alta de la Unidad de Cuidados Intensivos de un hospital de tercer nivel en la ciudad de Pereira, Risaralda, Colombia.

Conclusiones: La intoxicación por fluoroacetato de sodio es relativamente poco frecuente y puede causar injuria renal aguda y falla multiorgánica con alta tasa de complicaciones y muerte. Se presentó un caso de intoxicación autoinfligida que recibió terapia de reemplazo renal continua temprana con un desenlace favorable en términos de supervivencia en la UCI.

Palabras clave: Venenos, Envenenamiento, Toxicológica, Fluoroacetato de sodio, Falla renal aguda

Introduction

Sodium Fluoroacetate poisoning poses a diagnostic challenge for healthcare personnel caring for patients with signs and symptoms secondary to toxicity from this compound. Despite being a prohibited substance in Colombia, it is widely used for rodenticidal purposes in the country. There are few reviews on the subject, so it is necessary to know fundamental aspects of the substance, mechanism of action, determination methods in the clinical laboratory, and management of these patients (1).

Case report

A 14-year-old patient with no significant personal or family history was admitted into the emergency department. The patient was referred from the local unit because of the clinical condition of seven hours of evolution consisting of voluntary intake of sodium fluoroacetate for suicidal purposes. In the first level of attention, gastric lavage and oral doses of activated carbon were administered; It evolved inadequately with increased dyspnea and desaturation; given this, the patient is transferred to the third level of care.

The patient entered the third level of attention in quite feeble general conditions, desaturated, sialorrhea, and with a Glasgow coma scale of eight, fasciculations, and hypotension. It was decided to secure the airway to avoid the risk of the patient's bronchoaspiration and the alteration of the state of consciousness. Treatment with ethanol, calcium gluconate was started on the patient and transferred to the ICU.

Upon admission to the intensive care unit, the patient with unfavorable conditions presented Blood Pressure: 69/40 mmHg, Average Blood Pressure: 50 mmHg, Heart Rate: 116 per minute, Temperature: 36 °C, diaphoretic; thus, vasopressor support with Norepinephrine was started although the blood pressure goals were not achieved. In view of this, the patient required vasopressin to reach the goal during the first 24 hours of evolution. Mechanical ventilation assisted mode volume control, PEEP 6 FIO₂ 100%, glucometry: 137 mg/dL. Physical examinations showed hypochromic conjunctiva, normoreactive isocoric pupils, dry oral mucosa, mobile neck, thorax: rhythmic heart sounds without murmurs, tachycardia, decreased vesicular murmur in both fields with bibal crepitus, depressible soft pain without peritoneal irritation, extremities without edema, capillary refill in four seconds neurological RASS -5

The patient behaved anuric during the first 12 hours of the stay in the ICU, with levels of nitrogen containing compounds within normal limits, with persistent hyperlactatemia metabolic acidosis, multifactorial, secondary to intoxication per se. The use of ethanol

was established as medical management; kidney injury rapidly progressed to KDIGO III acute kidney injury, the reason why it was decided to start renal replacement therapy with continuous venovenous hemodiafiltration. In the Table 1 you can see the laboratory report:

Table 1. Laboratory report

LABORATORY TESTS	March 22/ 2017.	March 23/ 2017.	March 24/ 2017.	March 25/ 2017	March 26/ 2017
<i>BLOOD COUNT</i>	White blood cell count 23130 N 87 % HB 15 HCTO 44 Platelets 329.000	White blood cell count 11650 N 86 % HB 13 HCTO 38 Plate- lets 388.000	White blood cell count 14500 N 75 % HB 11 HCTO 33 Plate- lets 268.000	White blood cell count 11350 N 81 % HB 9,2 HCTO 26 Plate- lets 156.000	White blood cell count 9700 N 79 % HB 8,1 HCTO 23 Platelets 138.000
<i>UREIC NITROGEN IN BLOOD</i>	15 mg/dl	11 mg/dl	5 mg/dl	5 mg/dl	5 mg/dl
<i>CREATININ</i>	0.5 mg/dl	1.0 mg/dl	0.4 mg/dl	0.4 mg/dl	0.4 mg/dl
<i>SODIUM</i>	144 mmol/L	137mol/L	131mol/L	131mol/L	135mol/L
<i>POTASSIUM</i>	3,1 mmol/L	3.50 mmol/L	3.20 mmol/L	3.20 mmol/L	3.1mmol/L
<i>CHLORINE</i>	104 mmol/L	105.0 mmol/L			
<i>PHOSPHORUS</i>	6,1 mg/dl				
<i>MAGNESIUM</i>	1,9 mg/dl	1.6 mg/dl			
<i>CALCIUM</i>	1.22 Ionic 7.2 mmol/L				
<i>PREGNANCY TEST</i>	NEGATIVE 2.39 mUI/ml				
<i>PCR</i>	18mg/dl		14.9 mg/dl	27mg/dl	24.0 mg/dl
<i>COAGULATION TIMES</i>	PT 11 Seg. PTT 28 Seg. INR 0.91	PT 19 PTT >240 INR 1,3	PT 25.3 PTT >240 INR 1,68		PT 17 PTT 31 INR 1,18
<i>LIVER PROFILE</i>	AST 56 ALAT 67 U/L Total Bilirubin 0.4 mg/dl	TOTAL BILIRRUBIN 1.0 ALKALINE PHOS- PHATASE 115 TGP 62 TGO 99 U/L	TOTAL BILIRRUBIN 0.9 AMYLASE 391 U/L A L K A L I N E P H O S P H A T A S E 146 U/L TGP 71 U/L TGO 107 U/L		TOTAL BILIRRU- BIN 1,4 TGP 54 U/L TGO 58 U/L
<i>ALBUMIN</i>	5,1 gr/dl	2,2			
<i>ARTERIAL GASES</i>	pH 6.98 pCO2 50 pO2 277 HCO3 11be - 19.85 Lactate 7.4 PAFI 277	ARTERIAL GASES L:PH: 7.14, PO2: 98 MMHG, PCO2: 25 MMHG, HCO3: 8.5 MMOL/L, BE: -18.9 MMOL/L, PAFI: 280. SAO2: 95% LAC- TATE: 8.1 (----- ***** VE- NOUS GASES:PH: 7.30, PCO2: 35 MMHG, PO2: 47 MMHG, HCO3: 17.2 MMMOL, BE: -9.2 MMOL/L, SVO2: 78%	ARTERIAL GASES: PH:7,30 PCO2: 29 PO2:109 LAC:6,8 BI- CARBONATE: 14,3 PAFIO2: 272.	ARTERIAL GASES: PH: 7,46, CO2: 34, HCO3: 24,2, LACTA- TE: 2, PAFI: 206	ARTERIAL GA- SES PH 7.50 PCO2 35 PO2 96 HCO3 27 LACTA- TE 0.7 PAFI 336 VENOUS SATU- RATION 67%

As a management protocol was established with a dose of ethanol of 0.1 gr / kg, / hour, calcium infusion of 3 mg / k / h, hydric resuscitation, and vasoactive support for a target of mean arterial pressure greater than 65 mmHg in relation with distributional shock. The patient presented clinical evolution towards improvement after 72 hours of renal replacement therapy in terms of diuresis parameters and the resolution of metabolic acidosis with lactate clearance to normal levels; in view of this, the renal replacement therapy was discontinued. Clinically, vasoactive supports were withdrawn at the same time of evolution and towards the seven day of the patients' hospital stay, attempts were made to release mechanical ventilation, without any success. Synchronously, there were found febrile episodes and microbiological reports of staphylococcus aureus growth which was attributed to a pneumonic process that was covered with an antibiotic scheme treatment. After 10 days of management, the patient was discharged from the intensive care unit with a satisfactory evolution.

Discussion

The sodium fluoroacetate is known in Colombia as "Guayaquil" liquid, you can see it in Figure 1:



Figure 1. Sodium fluoroacetate's poisoning

In the United States, it is known as compound 1080. This poison was developed in 1940 by Marais when observing the effects that it produced in the goats such as the paralysis of the animal's posterior; consequently, it was called the "rear bankruptcy". It was later used as a rodenticide that was considered one of the most toxic substances in the world (1), its distribution and use in Colombia is prohibited (2).

The sodium fluoroacetate is a substance widely used in Colombia as a rodenticide and in some cases also as a way of committing suicide. In its 100% pure form it is a white powder that, when dissolved in water, forms an odorless,

colorless and tasteless solution, it is generally found on the market mixed with a blue dye to differentiate it from other substances. The lethal dose for humans is between 2 and 10 mg / kg. Due to its illegality, the concentrations in commercial products are irregular and therefore it is very difficult to determine the exact dose that the intoxicated people ingested. It is a fat-soluble substance with good oral absorption and with rapid distribution to the tissues after ingestion. The highest concentrations are found in plasma followed by kidney and muscle and the lowest concentration in the liver (3).

After the intake of the sodium fluoroacetate, it requires the metabolic conversion of fluoroacetate to fluorocitrate, obtaining increased levels thirty minutes after the ingestion of it, and with a maximum peak at four or six hours, and returning to basal concentrations at 40 hours. Its excretion is renal and takes between one and four days.

Sir John Peters in 1963 described the main effect of the sodium fluoroacetate consisting of ATP depletion, by inhibition of the tricarboxylic acid cycle or Krebs cycle (KC) (4). Sodium fluoroacetate reacts with the enzyme citrate synthase to form monofluoroacetate instead of citrate, a substance that is not a useful substrate for the enzyme aconitase in the Krebs cycle and therefore blocks it. The reduction in the oxidative metabolism contributes to lactic acidosis, which added to the accumulation of ketone bodies and the non-oxidation of fatty acids, brings an increase in acidosis (1). Despite its high metabolism, it accumulates less citrate and frequently affects the brain, heart, kidney, spleen, and liver.

The accumulation of citrate generates an electrolyte and acid-base imbalance, which leads to metabolic acidosis. The accumulation of lactate and cerebral citrate has been considered a cause of coma and seizure in the patient poisoned by fluoroacetate. Hypocalcemia is related to the chelating effect of fluorine, citrate, and fluoroacetate ions on calcium (1).

Initially, most patients are asymptomatic, but in a few hours they will present nausea, vomiting, sialorrhea, mydriasis, and electrolyte imbalances (especially hypocalcemia due to the chelating properties of calcium in sodium fluoroacetate), as occurred in the clinical case described. Central nervous system compromise occurs frequently as a diverse manifestation from drowsiness, vertigo, fasciculations, tremor, seizures and respiratory failure of central origin as occurred in this case. However, the cause of respiratory failure due to community-acquired pneumonia or initial shock is not ruled out. At the cardiovascular level, it was manifested in the patient with arrhythmias, prolongation of the QTc segment and less frequently myocarditis (5),(6) hypotension that could be due to the blockage of the tricarboxylic acid

cycle, and acidosis in the vascular epithelium. Death is generally caused by cardiopulmonary abnormalities. The diagnosis is made based on a clinical history that confirms the ingestion of substances containing sodium fluoroacetate and the presence of symptoms and signs described by various authors for this toxicosis (2),(7),(8).

Treatment

In the case of sodium fluoroacetate poisoning, the initial approach should be carried out as in all intoxicated patients; it is essential to take into account the initial ABCD, determining the need to obtain a definitive airway, correcting hemodynamic instability, and determining the oxygen and glucose supply of these patients (9). Management of support and correction of hypokalemia is essential. Different antidotes have been studied; however, the progress in humans is limited (10), (13). The management of seizures should be done with benzodiazepines, of which diazepam is the most recommended. In the case that the crisis does not stop, barbiturates such as thiopental should be used, which would additionally act as a brain protector, reducing the risk of cerebral edema and local ischemia (3). In the initial decontamination, the removal of contaminated clothing and external washing with soap and water is essential, as well as gastric lavage if the patient is admitted with less than one hour of oral exposure. Activated carbon has been shown to adsorb fluoroacetate; nonetheless, there is no data on the impact of the clinical outcome of these patients. Hemodynamic management should be performed with intravenous fluids, followed by vasopressors (norepinephrine) in cases where hypotension is not treated. The presence of hypotension, acidemia, and creatinine elevation is correlated with high mortality; therefore, these disorders must be managed promptly (14),(15). The most important electrolyte disorder is hypocalcaemia, which must be properly determined and treated in these patients. Improvement in survival has been found in animals when calcium chloride supplements are administered, although the results are not conclusive. Calcium has been reported to be useful in improving muscular activity (tetanic convulsive movements) and in cardiac arrhythmias (11).

Antidotes

The use of antidotes in sodium fluoroacetate poisoning is based on the need to prevent the production of fluorocitrate and inhibition of aconitase while achieving mitochondrial citrate output. In this order of ideas, acetate donors such as ethanol and glycerol monoacetate are the most widely used antidotes in the management of this poisoning. Ethanol has shown the best results and is the most used, its oxidation produces elevation of acetate levels, which competes in the formation of fluorocitrate (1), (16), (3),(9).

Several protocols have been proposed for the management with ethanol, it has been described that after the acute administration of fluoroacetate, 40 - 60 cc of 96% ethanol should be administered, followed by 1.0 - 1.5 g / kg of ethanol 5-10% intravenous in the first hour and subsequently 0.1 g / kg every hour for 6 - 8 hours (3). The exact dose of ethanol has not been determined, the most logical possibility is to achieve a serum ethanol concentration of 100 mg / dl, administering the same doses used in ethylene glycol and methanol poisoning (8).

Ethanol does not only block the production of fluorocitrate, but also decreases hyperglycemia and increases GABA levels in the central nervous system (3). In animal studies, the best results in methanol management are obtained after 10 min of fluoroacetate poisoning (7). Glycerol monoacetate and acetamide have been proposed as antidotes, animal studies that have been developed demonstrate the effectiveness in decreasing ketone body levels, decreasing citrate in the brain, kidney and heart, and improving neurological and cardiac effects. However, in humans an increase in hyperglycemia, worsening of metabolic acidosis, damage to capillaries and erythrocyte hemolysis are noted. Therefore, some reviews do not recommend the use of glycerol monoacetate or acetamide in the management of fluoroacetate poisoning in humans (3).

Other antidotes have been tried to develop in order to produce energy by supplying intermediates of the tricarboxylic acid cycle while blocking the production of fluorocitrate. The use of calcium salts (calcium gluconate), sodium succinate, and α -ketoglutarate have been evaluated, which have shown benefit as long as calcium is administered simultaneously, which shows the importance of stabilization of hypocalcemia in these patients (3),(11). The most effective regimen appears when administering 240 mg / kg sodium succinate and 130 mg / kg calcium gluconate fifteen minutes after administration of fluoroacetate (7),(16).

Renal replacement therapy

There are three techniques for eliminating toxins: hemodialysis, hemofiltration, and hemoperfusion (17),(18). Nevertheless, hemodialysis is the most adequate to eliminate low molecular weight and water-soluble toxins, which was used to treat this patient. Given the persistence of symptoms such as anuria for 12 hours, severe metabolic acidosis that was associated with the ingestion of the poison, a timely initiation of renal replacement therapy was decided (18),(19). The decision to start this therapy to treat the acute kidney injury and the presence of intoxication with severe clinical manifestations of the toxin was made due to the unavailability of a specific antidote and its specification

of the renal route; additionally for the anuric condition of the patient that would have perpetuated the symptoms of poisoning.

Conclusions

Sodium fluoroacetate poisoning is relatively rare and can cause acute kidney injury and multi-organ failure with a high rate of complications and death. A case of self-inflicted poisoning that received early continuous renal replacement therapy with a favorable outcome in terms of ICU survival was presented. The favorable outcome of the patient was possible in view of the low dose of the toxin, to the implementation of initial decontamination measures, and to a timely management in the intensive care unit with renal replacement therapy. Long-term clinical outcomes are unknown since there was not a follow-up to this case.

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