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CASE REPORT

Case report: severe ethylene glycol poisoning and the challenges in its diagnosis

Relato de caso: intoxicação grave por etilenoglicol e os desafios no seu diagnóstico

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ABSTRACT

Introduction: Ethylene glycol (EG) is a liquid widely used throughout the world as an antifreeze. Many reports have shown accidental and intentional intoxication, and access to this alcohol is quite easy in Brazil. However, the diagnosis of EG poisoning is challenging for several reasons: inaccessible serum levels, non-specific manifestations, difficulties in collecting clinical history, all factors that can lead to a delay in beginning specific therapy, as well as worse clinical outcomes. **Case Report:** The present case reports on an accidental intake of this substance by a patient, known to be an alcoholic, and the steps taken from clinical investigation to specific treatment. **Discussion:** Considerations regarding diagnosis and treatment, with the use of a specific antidote (fomepizole or ethanol, according to availability), and indications for hemodialysis will be discussed later in this report. Poisoning by toxic alcohols can mimic different types of conditions and its outcome is highly dependent on rapid clinical assessment and beginning of treatment within an optimal time. **Conclusion:** The reported case demonstrates that a strong clinical suspicion of toxic alcohol poisoning authorizes treatment with a specific antidote to improve the patient's condition.

Keywords: Ethylene glycol; Poisoning; Acidosis; Antidotes.

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RESUMO

Introdução: O etilenoglicol (EG) é um líquido largamente utilizado como anticongelante em todo o mundo. Existem muitos relatos de intoxicação, acidental e proposital, e o acesso a esse álcool é facilitado em nosso país. O diagnóstico da intoxicação por EG é desafiador por diversos motivos: dosagem sérica inacessível, manifestações inespecíficas, dificuldades de coleta na história clínica, fatores que podem levar ao atraso do início da terapia específica e resultar em piores desfechos clínicos. **Relato de Caso:** Relatamos um caso em que houve ingesta acidental da substância por paciente sabidamente etilista, e as etapas desde a investigação clínica até o tratamento específico. **Discussão:** Considerações sobre o diagnóstico e tratamento com o uso do antídoto específico (fomepizol ou etanol, de acordo com a disponibilidade) e indicações de hemodiálise são discutidas posteriormente ao relato. O envenenamento por álcoois tóxicos pode mimetizar diversos tipos de afecções e seu desfecho é altamente dependente da suposição clínica rápida e instituição do tratamento em tempo ótimo. **Conclusão:** O caso relatado demonstra que uma forte suspeita clínica de intoxicação por álcool tóxico autoriza o tratamento com antídoto específico impactando diretamente o desfecho do quadro.

Palavras-chave: Etilenoglicol; Intoxicação; Acidose; Antídotos.

Introduction

Ethylene glycol (EG) is a colorless, odorless liquid with a sweet taste[1]. It is widely used throughout the world as an antifreeze[1]. It is part of the composition of several products in Brazil, such as: additives for radiator fluid, brake fluids, solutions used in the refrigeration industry, windshield washer fluids, solvents, cleaning products, among others[1]. There are many reports of ethylene glycol poisoning, the vast majority by oral route, be it by accidental contamination of alcoholic beverages or by an accidental or intentional ingestion of liquids that have EG in their composition[1,2]. The lethal dose of EG is around 1.5mg/kg of body weight, but with a wide variation[2]. Like methanol, EG is rapidly absorbed from the gastrointestinal tract and peak serum levels occur within one to two hours after ingestion[2].

Ethylene glycol poisoning is associated with a high degree of morbidity and mortality if not identified and treated quickly. Metabolized by alcohol dehydrogenase (ADH), the toxicity of this compound is mainly related to its metabolites glycoaldehyde, glycolic acid, glyoxylic acid, and oxalic acid, which can cause metabolic acidemia, neurotoxicity, acute kidney injury (AKI), and death[2,3].

The diagnosis of this poisoning is challenging, since, in Brazil, dosage of the substance and its metabolites are unavailable for treatment[1]. Clinical manifestations are nonspecific, and there is often no clear history of ingestion, especially during initial care, a factor that can lead to a delay in starting specific therapy and result in worse clinical outcomes[1-3].

The present study aimed to report a case of poisoning due to the accidental ingestion of water from a car radiator and discuss the challenges and importance of clinical characterization and anamnesis in the diagnostic definition of poisoning. The work was submitted to and approved by the institution's Ethics Committee, through Plataforma Brasil, logged under CAEE number: 67658923.7.0000.5119.

Case Report

A male patient, 69 years of age and a heavy drinker, was admitted to the Emergency Care Unit, taken by the Prehospital Care Service, after being found confused, tachydyspneic, and hypotensive (80x50mmHg) on a public street. Admitted with a Glasgow Coma Scale (GCS) 13, confused, with a blood pressure (BP) of 230x120mmHg; tachydyspneic, with Kussmaul pattern; tachycardic, with peripheral cyanosis; and capillary blood glucose of 175mg/dL.

Laboratory propedeutics was performed, which identified intense metabolic acidosis with an elevated anion GAP. Sodium bicarbonate replacement was implemented, but serial blood gases revealed refractory metabolic acidosis and impaired renal function, with no response to intravenous hydration. Eight hours after admission to the Emergency Care Unit, the patient experienced a reduced level of consciousness (GCS 7). Orotracheal intubation was performed quickly, without complications. After an hour of this procedure, volume-refractory hypotension developed, and intravenous norepinephrine was started.

In contact with a Toxicological Information and Assistance Center, the attending physician contacted the patient's family in an attempt to better clarify the case. The nephew who lived with him reported that the patient was a long-time heavy drinker, with high social vulnerability and who drank *cachaça* (sugarcane whiskey) daily, and that he used to drink 70% alcohol with currants when he could not find his preferred drink. He reported that he suspected that the patient had ingested a pink solution from a soda bottle, which contained car radiator fluid with ethylene glycol, which resembled the mixture he commonly ingested (Figure 1).

The suspicion of poisoning by toxic alcohol adding the refractiveness to the established treatment led to the transfer of the patient to the reference hospital. The patient was admitted to the unit in a sedated state, oligoanuric, hemodynamically unstable with vasoactive drugs, and well adapted to mechanical ventilation. Laboratory propaedeutics showed the persistence of severe metabolic acidosis, hypernatremia, and acute kidney injure (AKI) (Table 1). The patient had received around 2,000ml of 8.4% sodium bicarbonate at the Emergency Care Unit. Dialysis was recommended, along with the implantation of a double-lumen catheter (DCL) and transfer to the Intensive Care Unit (ICU).

In this context, due to intense metabolic acidosis, a widened anion gap, and report from a family member, the hypothesis of poisoning by toxic alcohol was reinforced, and the decision was made to start treatment with a continuous infusion of 10% ethanol guided by ethanolemia, with the aim of maintaining a serum ethanol level of 100 to 150mg/dL, a continuous infusion of sodium bicarbonate, and hemodialysis (HD) (Figure 2).

Ethanol treatment was maintained for 40 hours and during administration, ethanolemia was assessed every 2 hours. Details of the treatment performed are highlighted in Table 2.

Progressive improvement was observed with the suspension of amines, the correction of acidosis and hydroelectrolyte disorders, and extubation on the fifth day, along with a return of spontaneous diuresis and the suspension of HD (Table 1).

On the sixth day of ICU, the patient developed psychomotor agitation, attributed to alcohol withdrawal syndrome (AWS), and benzodiazepine was applied.

The patient was discharged after 17 days of hospitalization, with normalized renal slag and no neurological sequelae.

Figure 1. Substance ingested by the patient.

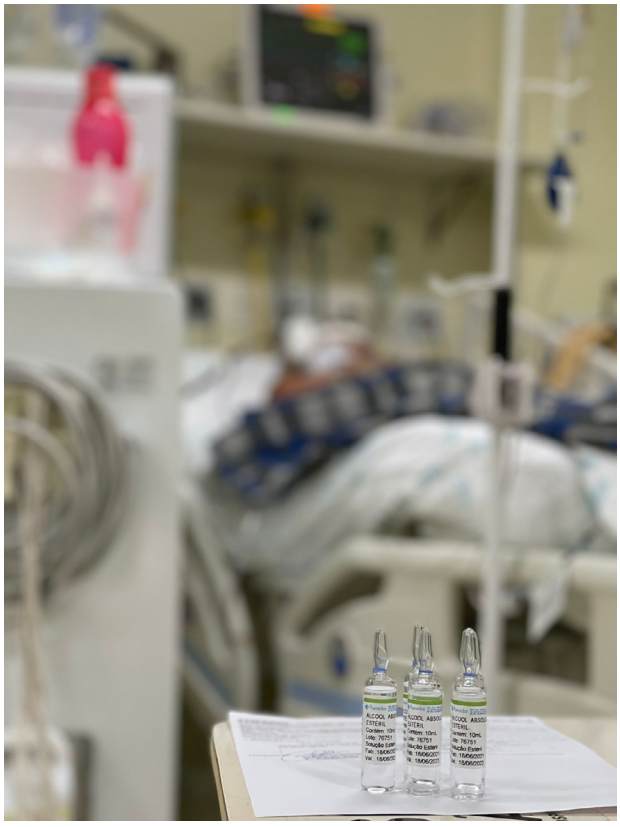

Figure 2. Administration of the antidote to the patient: critical moment of intervention with ethanol (antidote available).

Table 1. Patient laboratory progression.

Exam	Day 1	Day 2	Dia 3 Admission Reference Center	Day 4 After HD and ethanol	Day 5 Suspension of BIC and ethanol	Day 7	Day 8 ExToT Suspension of HD	Day 9	Day 15	Day 17 Discharge
Sodium Bicarbonate (mEq/L)	1.5	7	12	21	24.4	21.6	25.3	23.5		
pH	6.8	6.92	7.29	7.39	7.49	7.48	7.45	7.40		
Partial pressure CO_2 (mmHg)	9	44	30	35	32	29	34	38		
Partial pressure of O_2 (mmHg)	72	144	126	90	120	154	64	68		
Creatinine (mg/dL)	1.7	2.5	3.5	2.6	3.45	3.3	5.24	4.47	1.89	2.07
Oxaloacetic transaminase (U/L)	42	75			38					
Pyruvic transaminase (U/L)	19	25			19					
Urea (mg/dL)	28	47	87	28	64	78	109	84	59	84
Leukocytes (mm^3)	24.000	25080			6.100	3510	8310	10270	7310	
Sodium (mEq/L)	145	155	152	141	132	136	142	150	144	136
Potassium (mEq/L)	3.7	3.4	3.4	3.0	3.3	4.0	3.5	3.7	4.4	4.2
Lactate (mmol/L)	24	17	23	12	3.3	1	1.02	1.6		
Anion gap (mEq/L)			46	21						
Urine analysis			calcium oxalate ++							
Ethanol (g/L)	Remained entre 0.7 and 1.58 during the treatment									

Legend: CO_2 = Carbon dioxide; O_2 = Oxygen; HD = Hemodialysis; BIC = Sodium bicarbonate; EXTOT = Extubation.

Table 2. Treatment performed.

Treatment employed	Dose	Administration mode
Sodium bicarbonate	1-3 mEq/Kg intravenous until acidosis correction	133mEq of bicarbonate diluted in 250ml of 5% dextrose, at a rate of 150 to 250ml/h, should be discontinued when the patient reaches a pH>7.35. Potassium and sodium levels should be monitored.
Ethanol	Starting dose: 0,6-1,0 g/Kg (7,5-12,5ml of 10% ethanol solution in glucose/Kg Maintenance dose: 1.4ml of 10% ethanol solution/kg/h. Maintenance dose during hemodialysis: 3.3ml of 10% ethanol solution/kg/h	Dilution: 50 ml of 100% Ethanol in 450 ml of 5% dextrose. Perform serum ethanol dosage every 2 hours. Serum concentration should be maintained between 100-150mg/dL.

continued...

... continued Table 2

Treatment employed	Dose	Administration mode
Hemodialysis	Dialysis is indicated in patients who present metabolic acidosis with pH<7.30 despite treatment, deterioration of vital signs despite aggressive supportive care, renal failure or severe hydroelectrolyte disorders.	Adjusting the dose of ethanol to be administered during dialysis is essential, as is monitoring ethanolemia.
Adjuvant treatment	Use of amines in usual doses to treat shock, correct electrolyte disorders.	Monitorize capillary blood glucose every 1/1 to 2/2 hours during ethanol administration, periodic blood gas analysis (4-4 to 6-6 hours) to evaluate ions and acidosis.

Discussion

The ingestion of ethylene glycol and other toxic alcohols can occur both accidentally and through attempts at self-extermination and homicide[4]. Once ingested, the toxicity of ethylene glycol is related to its metabolization by the enzyme alcohol dehydrogenase (ADH), generating glycoaldehyde, which is subsequently converted into glycolic acid, glyoxylic acid, and oxalic acid[4].

Oxalic acid is capable of forming calcium oxalate crystals, which are deposited in various organs and can lead to renal, neurological, myocardial, and pulmonary dysfunction[1,2,4,5].

EG metabolites reach the kidney and lead to acute renal failure, which may be reversible, but this process can delay the elimination of ethylene glycol, creating a vicious cycle[5]. Renal failure is primarily due to glycolate-induced damage to the tubules, although obstruction of the tubules by precipitated oxalate crystals may also contribute to this condition[3,5]. Hypocalcemia in ethylene glycol overdose may result from the formation of calcium oxalate. Calcium oxalate crystals can be identified in urinalysis and corroborate the hypothesis of ethylene glycol poisoning[1,2]. EG, in the absence of treatment, has an estimated half-life of between three and nine hours[1,2,4].

Initially, the condition presented by the intoxicated patient is nonspecific, with a predominance of mental confusion, nausea and vomiting[6]. The initial clinical picture may be confused with ethanol intoxication[1,2,5]. The medical team must make every effort to identify the original source and nature of the exposure. EG poisoning is usually diagnosed clinically, in which there must be a strong suspicion or clear history of intake. Definitive diagnosis by gas chromatography is rarely available in time to guide treatment in Brazil. The presence of flank pain, hematuria, and oliguria suggest advanced ethylene glycol poisoning[5,6]. Cranial nerve palsy and tetany may also occur[2].

It is important to rule out differential diagnoses, as there are other causes of metabolic acidosis with increased anion gap such as diabetic ketoacidosis, toluene poisoning, salicylate poisoning, shock, for example[2]. Another important differential diagnosis, especially in chronic alcoholics, is alcoholic ketoacidosis[2,7]. Patients with a history of alcoholism and reports of recent drunkenness may present a condition that mimics the acidosis produced by toxic alcohols. Blood ethanol concentrations at this time may be low or undetectable. In alcohol withdrawal, high levels of catecholamines and cortisol amplify hormonal responses to fasting (low insulin levels, high glucagon), causing a marked increase in lipolysis. Increased peripheral release of fatty acids and delivery to the liver are necessary for the development of rapid ketogenesis. A low insulin/glucagon ratio is a prerequisite for hepatic fatty acid oxidation, so severe ketoacidosis usually occurs only after ethanol ingestion has ceased[2,7].

As EG is metabolized, metabolic acidemia appears after a latent period of approximately 3-6 hours after ingestion[2,4]. Thus, progressive neurotoxicity (coma, cerebral edema, cranial nerve palsy, and convulsions), tachycardia with hypertension or hypotension, respiratory distress, and acute renal failure may occur[3,4].

The minimum lethal doses of ethylene glycol are not well defined and, although it has been reported as approximately 1g/kg of body weight, there are reports in the literature of deaths caused by the ingestion of even smaller amounts, as well as survival after the ingestion of larger amounts[2,3]. It is well-known that there are several factors that can affect this variability, including the degree of dilution of the product, concomitant alcohol intake, the occurrence of vomiting and the patient's previous renal function[8]. However, every patient suspected of having ethylene glycol poisoning has a high chance of complications and a risk of death if not treated in a timely manner[2,8]. In this sense, a patient with an altered mental state, associated with a history of alcohol intake, easy access to products with ethylene glycol, and acidotic breathing deserves consideration of this potentially deadly ingestion.

Once ingested, ethylene glycol is quickly absorbed, and within a maximum of two hours, serum concentrations are already reached, a factor that leads to gastric lavage being discouraged for patients who arrive after this period of time[1,2]. Activated charcoal, gastric lavage, and ipecac syrup have no role in managing exposure to toxic alcohol[1,2].

Mortality from EG poisoning varies greatly due to differences in the amount ingested and the time elapsed since the beginning of specific treatment[8]. The highest mortality rate is found among patients with intense metabolic acidosis (pH<7.1) and the longest time elapsed after exposure and beginning of treatment (greater than 10 hours)[2,8].

Upon admission of the patient in question, despite family reports of heavy alcohol consumption, there was, initially, no history of ethylene glycol intake. The patient was admitted in a confused state, and, upon laboratory review, presented intense metabolic acidosis with a high anion gap. Despite the administration of sodium bicarbonate, serial blood gases on admission revealed metabolic acidosis refractory to bicarbonate replacement. The patient's clinical and laboratory conditions, associated with the history of heavy alcohol consumption – including a previous report of ingesting 70% alcohol with currant – and the social vulnerability experienced by the patient raised the suspicion of a possible intake of toxic alcohol. After other contacts with family members, the existence of car radiator fluid (with EG in its composition) in the residence was confirmed, and the suspicion of poisoning was promptly raised and specific treatment was begun. The similarity of the product with the drink that the patient used to drink, and the fact that it was packaged in non-original packaging normally used for drinking, contributed to the accidental intake.

The presence of metabolic acidosis with an increased anion gap, refractory to usual measures, in a patient suspected of intoxication, heavily indicates toxic alcohol intake[2]. Patients with ethylene glycol poisoning may experience elevations in serum lactate concentration. The presence of oxalate crystals in the urine corroborates EG poisoning, but is not pathognomonic, and care must be taken not to misinterpret positive or negative results[1,4,5].

The management of patients poisoned by toxic alcohols consists of general supportive measures, mainly actions for clinical stabilization and correction of acidosis, specific antidotes, and hemodialysis[8].

Currently, there are two antidotes for the treatment of EG poisoning. Ethanol has been used as an antidote since the 1960s and is the only antidote available in Brazil[1,8]. Fomepizole was approved in the USA in the 1990s, and where it is available, it has replaced ethanol as an antidote, as its administration is much easier and requires less back-up in the toxicology laboratory to control serum ethanol levels[8]. One must also consider the lower number of adverse reactions when compared to ethanol used as an antidote[8].

Ethanol is included in the Brazil National Antidote Policy as a treatment for toxic alcohol poisoning[9], but there is no distribution through the Ministry of Health. Currently, access to the substance is through compounding pharmacies, according to the health institution's interest in making it viable. Although access to the antidote is not difficult, the use of ethanol without periodic dosing of the patient's ethanolemia makes the procedure risky and harmful[2,6]. Therefore, even with access to the antidote, if there is no way to measure serum ethanol every 2 hours, the treatment is unfeasible.

Both antidotes are most effective when administered in the early phase of intoxication, before significant levels of toxic metabolites are observed[8]. A condition that once again highlights the importance of quickly identifying and addressing a suspected case of toxic alcohol poisoning. In addition to general support measures and the specific antidote, hemodialysis is important in the treatment of poisoning by toxic alcohol, given that, in addition to removing toxic metabolites and the not yet metabolized compound, it can act in the correction of metabolic acidosis and hydroelectrolyte disorders[1-4,8].

The dose of antidotes (fomepizole or ethanol) needs to be adjusted during hemodialysis, as both are dialyzable[2,8]. Interruption of dialysis is recommended when the anion gap is less than 18mmol/L or recommended if the serum EG concentration is less than 4mmol/L[2,8]. The dose of fomepizole is 15mg/kg, applied intravenously, followed by 10mg/kg every 12 hours, with adjustments for hemodialysis or after more than two days of treatment[7].

If ethanol is chosen, a loading dose of 10mL/kg of a 10% ethanol solution in a 5% glucose solution is recommended[1,2,8]. The loading dose should be administered over 60 minutes in order to avoid excessive side effects (e.g., hypotension, respiratory depression, drowsiness)[1,2]. A maintenance dose of 10% ethanol solution, starting at 1mL/kg per hour, is appropriate to maintain any current ethanol concentration[1,2]. This maintenance rate can be adjusted according to serial ethanol concentrations and increased by approximately 50% during hemodialysis. Ethanol concentrations should initially be measured every one to two hours[1,2].

In the absence of significant metabolic acidosis or renal failure, dialysis treatments can be avoided without adverse outcomes for the patient if alcohol dehydrogenase inhibitors are used[6,8]. In addition to specific antidotes, thiamine and pyridoxine can be used to facilitate the conversion of glyoxylate to non-toxic metabolites instead of oxalate[2,8].

Conclusion

The diagnosis and management of EG poisoning in patients is, therefore, a major challenge in emergency services. It can mimic different types of conditions and its outcome is highly dependent on rapid clinical suspicion and the beginning of treatment in an optimal time.

In the case described, despite initially having no history of intake, the patient was managed assertively, and after diagnostic suspicion, he received specific measures that improved his clinical manifestations. This case illustrates that a strong clinical suspicion of toxic alcohol poisoning justifies the use of a specific antidote, which can significantly influence the patient's outcome. Prompt administration of the antidote is crucial in improving recovery prospects and underscores the importance of timely intervention in cases of suspected toxic exposures.

Authors' Contributions

We describe contributions to the papers using the taxanomy (CRediT) provide above:

Conceptualization, Investigation, Methodology, Visualization & Writing – review and editing: JSA; AAF. *Project Administration, Supervision & Writing – original*

draft: PHOP; AAF. *Data Curation and Formal Analysis*: NDN. *Data Curation and Research*: AJMC.

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