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Case Report

Methanol Intoxication: The Importance of Early Diagnosis

Case Reports and Literature Review of Methanol Intoxication´s Diagnosis and Treatment

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ABSTRACT

Methanol intoxication is an unfrequent condition associated with high morbidity that can cause severe metabolic disturbances, blindness, and important neurological dysfunction potentially life-threatening. Therefore, early diagnosis and treatment is required to obtain the best possible result for the patient. Recently, an increase in cases of methanol intoxication has been observed in our environment (50% in the last year) and in our hospital, as in most of them, specific analysis techniques for methanol are not available.

That is why in this article we present four recent clinical cases that occurred in our hospital: to analyze the most relevant information derived from the management of these patients and their clinical and laboratory data. Our objective is to develop a valid strategy in order to facilitate obtaining an early diagnosis sometimes difficult to achieve.

Due to the potential mortality of this poisoning and the existence of treatment, it is important to recognize methanol intoxication immediately. After analyzing the exposed clinical cases, the results indicated that a high index of suspicion and the presence of metabolic acidosis associated with an elevated anion gap and osmol gap are characteristic findings that allow an early diagnosis.

Keywords: Methanol; Intoxication; Metabolic acidosis; Anion gap; Osmol gap

INTRODUCTION

Methanol (CH_3OH), also known as methyl alcohol, wood alcohol, or burning alcohol, is a colorless, volatile liquid at room temperature. It is harmless by itself, but its metabolites are extremely toxic [1]. Its use is common in industrial, laboratory and home products, as a component of various substances (antifreeze, solvents and fuels). Its clandestine use in the production of adulterated alcoholic beverages usually leads to acute poisoning. Although described cases of methanol intoxication are sporadic, the mortality is usually very high. Toxic exposure occurs predominantly orally, although inhalation or transdermal absorption can also lead to poisoning. Susceptibility to the toxic effects of methanol is variable, but taking a small amount can lead to serious intoxication. There is great variability in the dose considered toxic and lethal, although most authors consider the lethal dose to be 30 mL of pure methanol [1,2].

Poisoning, both accidental and suicidal, has a high morbidity and mortality, due in most cases to the difficulty confirming the diagnosis, which delays the onset of treatment. This treatment should be started with the slightest suspicion of the clinical condition, with an analytical approach based on laboratory results (anion gap and osmol gap), and without waiting for analytical confirmation of methanol value. The early administration of therapeutic measures is crucial in order to limit the damage and enable a potential recovery of the patient [1-4].

Lately, there has been an increase in cases of methanol intoxication

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in our environment. Due to the difficulty observed in the management of these cases, we want to emphasize the importance of carrying out diagnostic evaluation properly and as early as possible. In this work we have compiled four cases diagnosed in our hospital in which osmol gap analysis was decisive in order to correctly guide the diagnosis. We consider essential to give value to this test and promote its analysis in the early diagnosis of methanol intoxication.

CASE PRESENTATION

First case

A 48-year-old woman with history of compulsive alcoholism was referred from her health center to the Emergency Department for probable methanol poisoning. Her partner reported that the day before she had signs compatible with alcoholic intoxication that persisted until the night and in the morning she had woken up ataxic, with a slight blindness and incongruous speech. He could not find alcoholic beverages at home, just an empty methyl alcohol bottle.

In the initial examination, deterioration in the level of consciousness, Kussmaul respiration, cold skin and cyanosis stood out: blood pressure 150/100, temperature 31.5ºC, tachypneic but O_2 saturation of 97%. ECG and chest X-ray without alterations. She had no eye opening, no verbal response and no motor response. Bilateral nonreactive mydriasis was seen.

Gasometry showed severe metabolic acidosis with a pH <6.8, incalculable bicarbonate, lactate 7.1 mmol/L, sodium 147 mmol/L, chlorine 105 mmol/L and potassium 4.21 mmol/L. In the biochemistry, glucose 158 mg/dL, urea 20 mg/dL, lactate dehydrogenase 1043 U/L, alanine transaminase 668 U/L and ethanol <0.1 g/L stood out, and in the hemogram, leukocytosis $11.03*10^3/\mu L$. She had a high anion gap (46 mmol/L) and a high osmol gap (90 mOsm/kg) [Reference values are shown in the table 1]. The rest of laboratory parameters were normal. Given these results, the suspicion of methanol poisoning was reinforced and the patient was admitted to the Intensive Care Unit (ICU) to receive the treatment, requiring mechanical ventilation, serum therapy, antidote with intravenous ethanol, sodium bicarbonate and folic acid, and hemodialysis to purify methanol molecules. After 6 hours of hemodialysis, metabolic acidosis was corrected and ethanol treatment was removed.

The definitive diagnosis was confirmed with the determination of plasma levels of methanol by gas chromatography: 3,062 g/L (indicative reference value: toxic level >0.2 g/L). Surprisingly, the woman recovered from the episode despite the high amount of methanol consumed. A second sample extracted after 4 hours of hemodialysis was analyzed, the result of which was: 0.324 g/L. After several hours of metabolization and 4 hours of treatment, methanol was practically undetectable in the patient´s blood. These data helped us to better understand the analytical characteristics of methanol intoxication, giving importance to its early detection.

Second case

A 62-year-old man, habitual drinker, was admitted to the Hospital due to a decreased level of consciousness. According to his family, he had been drinking alcohol for 3 days with little food intake. He had had a worsening of the level of consciousness, with vomiting and progressive drowsiness. After spending hours sleeping, they noticed him making strange incoherent noises, reason why they called Emergencies.

In the initial examination, deterioration in the level of consciousness, agonizing breathing, cold skin and dehydration stood out: blood pressure 100/80, temperature 33.8ºC and O_2 saturation of 97%. His condition was poor with Glasgow 3/15, and bilateral nonreactive mydriasis was seen. Suddenly, he presented cardiorespiratory arrest that required resuscitation of approximately 20 minutes. Once the pulse was recovered, brain and thoracic computed tomography scans were performed without any findings.

Gasometry showed severe metabolic acidosis with pH 6.86, bicarbonate 7 mmol/L, lactate >20 mmol/L, sodium 146 mmol/L, chlorine 80 mmol/L and potassium 5.01 mmol/L. In the biochemistry, glucose 255 mg/dL, urea 93 mg/dL, NT-proBNP 1779 pg/mL, alanine transaminase 74 U/L, creatine kinase 1191 U/L and ethanol <0.1 g/L stood out, and in the hemogram, leukocytosis 18, $57*10^3/\mu L$. He had a high anion gap (64 mmol/L), but it was not possible to determine the osmol gap, due to lack of osmolality data measured by osmometer [Reference values are shown in the table 1].

His clinical evolution was torpid. Vasoactive and respiratory supports were provided. He showed little response to treatment: in blood analysis, coagulopathy and acute renal failure were observed. Optimization of treatment with serum therapy, bicarbonate and progressive increase in vasopressors was attempted, but shock and refractory metabolic acidosis persisted. Given his history, clinical findings and metabolic acidosis with persistent high anion gap, the possibility of methanol intoxication was considered, so hemodialysis and intravenous ethanol were instituted. Despite treatment, the evolution was unfavorable with the appearance of acute respiratory failure and persistent irreversible shock, and at the end the patient died.

The post mortem report delivered one week later mentioned blood methanol levels of 0.006 g/L. Obtaining a very low result, the diagnosis could not be confirmed, but we remained suspicious of methanol poisoning. The organism could have been metabolizing methanol for 3 days since the exposure and the analyzed sample was extracted 4 hours after admission, so the treatment would have already done its work by eliminating the methanol.

Third case

A 57-year-old man presented at the Emergency Department due to poor general condition. Two days before, he had consulted for fever and acute pharyngitis and was treated with Azithromycin without improvement.

In the initial examination, cold skin, poor perfusion and stupor of two days of evolution stood out. His condition was poor with Glasgow 8/15, and bilateral nonreactive mydriasis was seen. He presented 3 episodes of cardiorespiratory arrest from which he recovered, and he was admitted to the ICU on suspicion of septic shock. The abdomen was soft and depressible, without signs of peritoneal irritation and he had no other signs that suggested an infectious focus or skin disorders.

Gasometry showed severe metabolic acidosis with a pH <6.8, incalculable bicarbonate, lactate 12.6 mmol/L, sodium 142 mmol/L, chlorine 98 mmol/L and potassium 5.3 mmol/L. In the biochemistry glucose 256 mg/dL and urea 54 mg/dL stood out,

Table 1: Patients´ first analytical results.

Parameters (Units)	Results				Reference values
	1st Case	2nd Case	3rd Case	4th Case	
pH	<6.8	6.86	<6.8	<6.8	[7.35-7.45]
Bicarbonate (mmol/L)	incalculable	7	incalculable	5	[21-28]
Lactate (mmol/L)	7.1	>20	12.6	>20	[0.30-2.00]
Sodium (mmol/L)	147	146	142	143	[135-145]
Chlorine (mmol/L)	105	80	98	89	[93-110]
Potassium (mmol/L)	4.21	5.01	5.3	5.8	[3.3-5.1]
Glucose (mg/dL)	158	255	256	292	[70-110]
Urea (mg/dL)	20	93	54	11	[10-65]
Lactate dehydrogenase (U/L)	1043	-	-	-	[135-250]
Alanine transaminase (U/L)	668	74	-	205	[0-33]
High-sensitivity troponin T (ng/L)	-	-	-	111	[0-14]
NT-proBNP (pg/mL)	-	1779	-	2481	[0-300]
Creatine kinase (U/L)	-	1191	-	-	[0-189]
White blood cells (*10^3/µL)	11.03	18.57	21.64	10.80	[3.8-10]
Anion gap (mmol/L)	46	64	44	49	[8-16]
Measured osmolality (mOsm/kg)	384	-	444	336	[282-300]
Calculated osmolality (mOsm/kg)	294	310	318	316	[275-301]
Osmol gap (mOsm/kg)	90	-	126	20	[<10]
Ethanol (g/L)	<0.1	<0.1	-	0.33	-
Methanol (g/L)	3.062	0.006	5.029	0.021	[0-0.005]

and in the hemogram leukocytosis 21.64*10^3/µL. He had a high anion gap (44 mmol/L). After several hours with metabolic acidosis refractory to treatment, methanol intoxication was suspected, intravenous ethanol was established and osmol gap is calculated, which showed a very high value (126 mOsm/kg) [Reference values are shown in the table 1].

We contacted the family, who reported that he regularly consumed alcohol and that they found a half-empty bottle of methyl alcohol at home. Despite the medical effort, the patient´s evolution was unfavorable and he died 2 days later.

The suspicion was confirmed with the determination of plasma levels of methanol by gas chromatography: 5,029 g/L. This was a very high result, which may mean that the patient had consumed a large amount of methanol. The definitive diagnosis was brain death from methanol intoxication.

Fourth case

A 46-year-old man was found by alcoholic beverage dealers disoriented, with altered behavior and tonic movements. They alerted Emergencies.

In the initial examination, disconnection from the medium, cold skin, hepatomegaly, splenomegaly, loss of body tone and tonic movements of the extremities stood out. He was able to keep his eyes open and mydriatic pupils were appreciated. He had low blood pressure (80/50) and O_2 saturation of 93%. He presented an episode of cardiorespiratory arrest and advanced cardiopulmonary resuscitation maneuvers were started. He recovered the central pulse after administration of adrenaline and midazolam.

Gasometry showed severe metabolic acidosis with a pH <6.8, bicarbonate 5 mmol/L, lactate >20 mmol/L, sodium 143 mmol/L, chlorine 89 mmol/L and potassium 5.8 mmol/L. In the biochemistry, glucose 292 mg/dL, urea 11 mg/dL, NT-proBNP 2481 pg/mL, high-sensitivity troponin T 111 ng/L, alanine transaminase 205 U/L and ethanol 0.33 g/L stood out, and in the hemogram, leukocytosis 10.80*10^3/µL. He had high anion gap (49 mmol/L) and high osmol gap (20 mOsm/kg) [Reference values are shown in the table 1]. Given these results, methanol intoxication was suspected and he was admitted to the ICU to receive treatment. Therapy with intravenous ethanol and hemodialysis was started, but the patient died within a few hours.

Methanol result was 0.021 g/L, confirming the diagnosis.

DISCUSSION

Methanol is rapidly absorbed from the digestive tract, giving plasma peaks in 30-60 minutes. It easily crosses the blood-brain barrier. Its serum half-life ranges from 12 to 24 hours. A small amount of methanol is found in the exhaled air of normal subjects due to endogenous metabolic production. In untreated patients, renal elimination is less than 5% and the rest is eliminated by hepatic biotransformation: it is oxidized by alcohol dehydrogenase generating formaldehyde, which is converted, by formaldehyde dehydrogenase, in formic acid and, subsequently, through folate-dependent oxidation, in carbon dioxide and water (Figure 1). The toxic effects of methanol overdose are due to the formation of these two metabolites, with formic acid being the main cause of ocular toxicity and metabolic acidosis with a high anion gap. In advanced stages of intoxication, lactate may form as a consequence of mitochondrial inhibition, exacerbating metabolic acidosis. Methanol by itself is not toxic; the toxic action depends on the amount of toxic metabolites that are formed [5].

The onset of symptoms is extremely variable and depends on the

dose of methanol, the rate of incorporation and the route of entry, and they can start between 30 minutes and 72 hours, although in most cases they appear in the first 12-24 hours, which is the time necessary for the biotransformation of methanol into its metabolites. Co-ingestion of ethanol delays symptoms. Mortality ranges from 25-50% of cases and the surviving cases usually present important neurological and visual sequelae, including blindness [6,7].

The symptoms and signs of intoxication can have different repercussions and can be grouped into:

a) Involvement of the central nervous system: In mild or moderate poisoning headache, dizziness, lethargy, ataxia or a state similar to alcohol intoxication occur. In severe cases, seizures, coma, and cerebral edema may appear. Selective neurotoxicity is the result of the hypoxia produced by formic acid after inhibition of cytochrome oxidase.

b) Ocular involvement: There is sudden loss of visual acuity and papillae edema with irreversible blindness due to optic nerve atrophy. Nystagmus and changes in pupillary reflexes may appear. Likewise, loss of vision, mydriasis with loss of the photomotor reflex and papillary edema can be developed.

c) Gastrointestinal involvement: Methanol is slightly irritating, which causes nausea, vomiting and abdominal pain; if the intoxication progresses, clinical and enzymatic data of acute pancreatitis can be developed.

Methanol does not produce pulmonary toxicity, except when inhaled.

For the suspicion of methanol intoxication diagnosis, the patient's history, clinic and laboratory data must be taken into account. The most characteristic data is metabolic acidosis with increased anion gap (>16 mmol/L), so it should be suspected in all situations that show this analytical result [8,9].

The diagnosis is confirmed by measuring blood levels of methanol, a determination that is not routinely available in most hospitals. However, in case of suspected methanol poisoning with compatible symptoms, metabolic acidosis and high anion gap, the measurement of other analytical data can be used to diagnose and manage the episode as soon as possible: the osmol gap (Figure 2). A high osmol gap result means the presence of osmotically active substances in blood, such as alcohols (methanol, ethylene glycol), sugars (mannitol, sorbitol), lipids (hypertriglyceridemia) or proteins (hypergammaglobulinemia). Therefore, the osmol gap value is used as a screening tool to identify toxics, and together with the clinical and analytical data previously mentioned, it is a determining measure in the orientation of the diagnosis of methanol intoxication and an aid for a rapid establishment of treatment. Furthermore, its calculation can also serve to estimate the approximate blood concentration of methanol (osmol gap x 0.032, in g/L). However, osmol gap value varies with time in cases of methanol poisoning: during the first hours, just after exposure to methanol, the osmol gap is high; but during the following hours, due to the metabolization of methanol in formic acid, the osmol gap normalizes. The opposite happens to anion gap: while the osmol gap decreases, the anion gap value increases with the time (Figure 3). Therefore, several hours after exposure, osmol gap may appear normalized and its measurement can lead to a false negative result and, consequently, to a diagnostic error. In all suspected cases, the diagnosis must be confirmed by blood determination of methanol. The result is usually positive in the analysis of samples collected in the first 24 hours after exposure, but may be negative in late diagnoses due to the degradation of methanol [10, 11].

The severity of poisoning is classified according to levels of methanol in blood, which correlate with the clinic in the following ways [12]:

Mild intoxication: Methanolemia (blood methanol) less than 0.2 g/L. Feeling of fatigue, nausea, epigastralgia, headache and visual disturbances of perception or accommodation.

Moderate intoxication: Methanolemia between 0.2-0.5 g/L. Vomiting, expressions of drunkenness, especially if the poisoning is mixed (ethanol-methanol), cold and sweaty skin, blurred vision and tachypnea, trying to make respiratory compensation for metabolic acidosis.

Severe intoxication: Methanolemia greater than 0.5 g/L. Comatose arrest, rapid and shallow breathing, seizures, peripheral and central cyanosis, hypotension, and papilledema.

Methanolemia greater than >1 g/L is considered lethal.

Within the differential diagnosis, all those entities that also

Anion gap (mmol/L) = $[Na^+] - [Cl] + [HCO_3]$

[Reference value: 8-16 mmol/L]

Osmol gap (mOsm/kg): Unmeasured ("unknown") remaining solute in blood

Osmol gap = [Measured osmolality] - [Calculated osmolality]

[Reference value: <10 mOsm/Kg; critical value: >15 mOsm/kg]

Measured osmolality: All osmotically active solutes in blood

Calculated osmolality: Expected osmotically active solutes in blood

$$Calculated\ osmolality = 2 \times [Na^+] + 2 \times [K^+] + \frac{[Urea]}{6} + \frac{[Glucose]}{18}$$

[Na^+ *in mmol/L*; K^+ *in mmol/L*; Urea *in mg/dL*; Glucose *in mg/dL*]

Estimated methanol blood concentration (g/L) = Osmol gap x 0.032

Figure 2: Anion gap and osmol gap calculation.

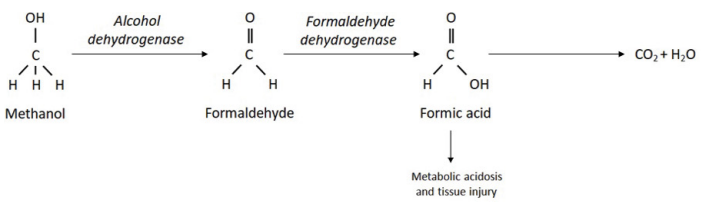

Figure 1: Methanol metabolization process.

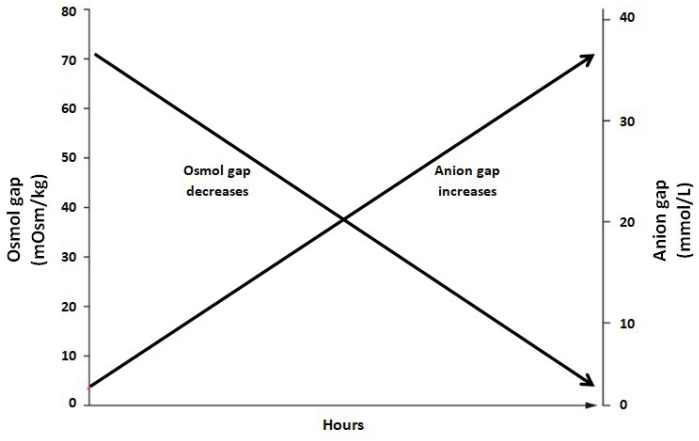

Figure 3: Time course of changes in osmol gap and anion gap.

produce metabolic acidosis with an increased anion gap should be considered (intoxication by salicylates, intoxication by ethylene glycol, alcoholic ketoacidosis, etc.) [13,14].

The evolution correlates better with the severity of the acidosis than with the serum concentration of methanol. The prognosis is better if the ingested dose has been divided over time, if ethanol has been ingested simultaneously or if appropriate treatment is applied early [15].

Given the high lethality of these cases, an intensive approach is recommended, delaying care as little as possible. Therapeutic measures include symptomatic treatment of complications, correction of acidosis, administration of ethanol to decrease the transformation of methanol into its toxic metabolites, and extraction of both methanol and its metabolites with dialysis. Adequate respiratory support with advanced airway management and mechanical ventilation should be provided if necessary. Intravenous solutions should be administered to maintain adequate hydro-electrolyte balance and urine output. Gastric lavage is only effective within the first two hours after ingestion. Activated charcoal, laxatives or cathartics are not effective in methanol poisoning [16-18].

Initially, it is advisable to start the administration of the antidote (ethanol) when we suspect significant methanol intoxication (>30 mL in adults and >0.4 mL/kg in children) and/or in the presence of metabolic acidosis and/or characteristic clinic, although we do not know the ingested dose or the levels of methanol. Ethanol is considered the treatment of choice, since it is metabolized by alcohol dehydrogenase, with a 10-fold higher affinity than methanol, so it produces a competitive inhibition blocking the formation of the two metabolites (formaldehyde and formic acid), responsible for the toxicity. Ethanol can be administered orally or intravenously (central line, given its high osmolarity). For achieving this therapeutic effect, plasma ethanol levels of 1-1.5 mg/mL must be maintained. This treatment requires monitoring of plasma ethanol values.

Nowadays, another antidote is available, fomepizole (4-methylpyrazole), which acts by competitively inhibiting alcohol dehydrogenase, with an affinity 80,000 times greater than methanol and 8,000 times greater than ethanol. It has no hepatotoxic effects and has some advantages over ethanol: it does not increase sedation on the patient, it has less risk of hypoglycemia, less problems with excess fluids, less problems in hemodynamically unstable patients, it is easy to handle and it can be administered both orally and intravenously. The great drawback of fomepizole is its high cost [19-24].

The use of bicarbonate not only improves metabolic acidosis, but also prevents the formation of formic acid. The infusion should be started when bicarbonate is less than 18 mEq/L. Sometimes, the required amount of bicarbonate is high (500-1,000 mEq/day), since patients relatively frequently have a pH below 7.0, which does not respond to bicarbonate treatment. Folic acid supplementation is required, since it is a necessary cofactor for the transformation of formic acid into H_2O and CO_2, thereby reducing the severity of eye damage. It has been shown to be effective if it is administered up to 10 hours after ingestion of methanol. Among the measures aimed at activating the extraction of methanol, hemodialysis is the most useful, since it purifies both methanol and its metabolites [25].

CONCLUSIONS

Methanol intoxication is currently a problem of great toxicological interest, given the severe metabolic acidosis with high anion gap and high osmol gap that causes and how fast it can lead to the development of complications and even death. This acidosis, as well as the sudden neurological manifestations, should guide the clinician to a rapid diagnostic suspicion. This is crucial, in order to start early intensive treatment, since both antidotes and hemodialysis management lose much of their efficacy when most of the methanol has been metabolized to its toxic products.

In an early detection of methanol intoxication, the clinical laboratory plays a crucial role, by alerting the clinician about the critical values, offering the possibility of realization of some useful laboratory determinations such as anion gap and osmol gap, and clearing up all the doubts that might emerge when interpreting the results of these determinations. In most laboratories, specific analysis techniques for methanol are not available, and there lies the importance of a rapid realization and a correct interpretation of these laboratory tests.

Osmol gap analysis has been shown to be effective for an early diagnostic approach to methanol intoxication. Because of this, it is essential to establish a fluid communication between the analyst and the clinician during all this diagnostic process.

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