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Review

Methyl Alcohol (Methanol) Intoxication

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Abstract: Methanol is a clear, colorless and highly toxic substance obtained from destructive distillation of wood. Methanol, which is generally used as solvent and antifreeze in industrial solvents, paints, varnishes, gasoline mixtures and automobiles, is a type of non-drinking alcohol due to its taste and odor. It can be produced as a by-product during the production of distilled alcoholic beverages. Accidental or suicidal ingestion of methanol may cause intoxication. Methanol often brings about oral intoxications. Methanol intoxication occasionally occurs in epidemics. Metabolites of methyl alcohol are toxic. Most of the symptoms of methanol intoxication are associated with metabolic acidosis. Symptoms are usually related to the central nervous system, eyes and gastrointestinal tract and may occur after a latent period. It may have serious consequences, such as blindness and death. Prognosis is correlated with the degree of metabolic acidosis. The toxic dose of methyl alcohol in human is in a wide range. Hemorrhage and necrosis in the basal ganglia and hemorrhage in the putamen are the findings obtained in radiological examinations and autopsy studies. Methanol levels in the blood of the autopsy cases are quite different. In our country, there has been a significant increase in the number of intoxication cases and deaths as individuals started to produce their own drinks or turned to fake drinks due to the increasing prices of alcoholic beverages. Not to increase the number of intoxication cases and deaths, the government should make the necessary arrangements and take precautions as soon as possible. This paper aims to evaluate all aspects of methanol poisoning and present it as a guide to forensic medicine specialists.

Keywords: Methanol, Methanol Toxicity, Death

Öz Metanol odunun destrüktif distilasyonundan elde edilen berrak, renksiz ve yüksek derecede toksik bir maddedir. Genellikle endüstriyel çözücülerde, boyalarda, verniklerde, benzin karışımlarında ve otomobillerde çözücü ve antifriz olarak kullanılan metanol, tadı ve kokusundan dolayı içilemeyen bir alkol türüdür. Distile alkollü içkilerin üretimi sırasında yan ürün olarak ortaya çıkabilmektedir. Metanolün kazara ya da intihar amacıyla alınması intoksikasyona neden olabilmektedir. Sıklıkla oral yoldan intoksikasyonlara neden olur, nadiren de inhalasyonla veya cilt yüzeyinden emilimle vücuda alınmaktadır. Metanol intoksikasyonu zaman zaman epidemiler halinde ortaya çıkmaktadır. Metil alkolün metabolitleri toksiktir. Metanol intoksikasyonunda semptomların çoğu metabolik asidoz ile ilişkilidir.Semptomlar genellikle santral sinir sistemi, gözler ve gastrointestinal sistem ile ilgilidir ve latent bir periyodun ardından ortaya çıkar. Körlük ve ölüm gibi çok ciddi sonuçları olabilmektedir. Prognoz metabolik asidozun derecesiyle koreledir. İnsanda metil alkolün toksik dozu geniş bir aralıktadır. Radyolojik incelemelerde ve otopsi çalışmalarında bazal ganglion kanaması ve nekrozu, putamende hemoraji elde edilen bulgulardır. Otopsi yapılan olguların kanındaki metanol düzeyleri oldukça farklılık göstermektedir. Alkollü içki fiyatlarında artış ile birlikte bireylerin kendi içkilerini üretmeye başlaması veya sahte içkiye yönelmeleri intoksikasyon vakalarında ve ölümlerde ciddi bir artışa neden olmuştur. İntoksikasyon olgularının ve ölümlerin daha fazla artmaması için toplumun bilgi düzeyini arttırmaya yönelik gerekli düzenlemelerin yapılması gerekmektedir.

Anahtar kelimeler: Metanol, Metanol İntoksikasyonu, Ölüm

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1. Introduction

Methanol was first isolated in 1661 by Robert Boyle by wood distillation and its chemical composition was first discovered in 1834 by Dümas and Peligot (1). Methyl alcohol (methanol) has the simplest structure among aliphatic alcohols. It is also used as a solvent in the industry (2).

Methyl Alcohol (Methanol CH3OH) is colorless, volatile liquid, which has a smell similar to ethyl alcohol and has a burnt flavor. The molecular weight of pure methanol is 32 g / mol, its appearance is colorless and clear. Its boiling point is 65 ° C. It is flammable and the flash point is 10 ° C. It is explosive when found in the air at a rate of 7.3-36.5%, while at 464 ° C it burns. Synonyms of methyl alcohol are as follows: methanol, methyl hydroxide, methyl hydrate, denatured alcohol, wood spirit and wood naphtha. Methyl alcohol is used as lacquer and varnish solvent in industry and as antifreeze in automobiles. It is used in the preparation phase of many organic materials (such as plastic paint, film) and, of course, alcohol denaturation (prepared by adding 5-10% methyl alcohol to ethyl alcohol) (3-5).

Methyl alcohol is a potentially alternative fuel. Therefore, it is predicted that its production will increase gradually. Methanol can be produced using several different carbon-based raw materials, such as natural gas, naphtha, heavy oil fractions and coal (4,5). The risk of exposure may increase due to its entry into the agenda as an alternative automotive fuel, in addition to its use in industrial products (5-7).

According to the Distilled Alcoholic Beverages Communiqué of Turkish Food Codex published in the Official Gazette No. 30014 dated March 21, 2017, distilled alcoholic beverage is a beverage prepared for human consumption, alcohol amount is at least 15% by volume at +20 ºC, produced by direct distillation of natural fermentation products with added or not added flavor and/or maceration of herbal substancesor blending of aromatic substances, sugar or other sweetening products in accordance with the Turkish Food Codex, into ethyl alcohol of agricultural origin or distillate or distillate beverages of agricultural origin.

While producing distilled alcoholic liquids, mainly methanol, aldehydes (acetaldehyde, acetal), esters (ethyl acetate, methyl acetate) and high alcohols (2-butanol, n-propanol, isobutanol, n-butanol 2-methyl-1-butanol, 3-methyl 1-butanol) are existing in the distillate of the alcoholic liquid formed by alcohol fermentation, other than water and ethyl alcohol. The amounts of these compounds, most of which are over a certain dose, toxic and harmful to health, should be kept within the limits considered to be health-safe in the final product. During production, the compounds are separated from each other by the distillation method by making use of the boiling points of these compounds. For this purpose, the distillate is divided into three parts as follows: the head, middle and end (tail) product. By separating the head product (with acetaldehyde, acetal, methyl acetate, ethyl acetate and methanol) with a lower boiling point than ethyl alcohol, and the end product with higher alcohols (2-butanol, n-propanol, isobutanol, n-butanol, 2-methyl-1-butanol, 3-methyl-1-butanol) with higher boiling point medium product rich in ethyl alcohol is taken and processed into raki. However, the compounds other than ethyl alcohol pass into the raki somewhat depending on the time of taking the middle product. Methanol, which is present in distilled spirits, consists of pectin through pectolitic enzymes while fermentation occurs. Pectin is found mostly in the peel and core of raisins and fresh grapes. During the production of alcohol, grape chips are included in fermentation along with the crust, core and stem. Therefore, the soluble pectic substances found in these parts pass into the gravel, are hydrolyzed by pectolitic enzymes, and as a result, methyl alcohol is formed (8).

According to the Tobacco and Alcohol Market Coordination Committee's (TAPDK) data, in our country, fully denatured and T-type denatured ethyl alcohol products contain certain amounts of methyl alcohol. Known by the people as blue spirit or white spirit used for cleaning is not pure methyl alcohol, although it is actually ethyl alcohol, but it also contains methyl alcohol due to denaturation transaction (9).

Household products containing methanol include automotive windshield washer fluids and de-icers, domestic spirits fuels, paints, paints, varnishes, wood dyes, paint reducers and removers, and a variety of other solvents. Also, not to consume ethanol, methanol can be added specially in it, and these products are called denatured alcohol (9,10).

The cost of methanol is much lower compared to other alcohols because it can be easily obtained by destructive distillation of wood. Because of this reason, consumption of products known to contain methanol by imposters into alcoholic drinks or accidental intake of these products by children may cause death (11,12). In addition, intoxications due to inhalation and skin toxicity have been reported rarely (13-16).

In our country, Turla et al. reported 124 deaths due to methanol intoxication in their study between 1992-1997, whereas İnanıcı et al. reported 205 deaths in another study between 1994-1998 (17-19).

In Eke et al.'s study between the years 2001-2004, by determining retrospectively the cases of forensic autopsy, which was performed over a 4-year period, the ethyl alcohol in 18 of and methyl alcohol in 22 of the 40 cases of alcohol intoxication were detected. When the source of methanol was investigated in cases with methyl alcohol intoxication, it was found that there were spirit alcohol in three cases, cologne in 10 cases, and spirit and cologne in one case. It was reported that information was not available in eight cases. In the study of alcohol levels, it was stated that it was in the range of 279-516 mg / dl in ethyl alcohol cases and 74-485 mg / dl in methyl alcohol cases (20).

Gülmen et al. in the retrospective study of autopsy cases between 1997-2003 in Adana, the findings showed that the source of the death of 41 cases was direct methanol poisoning (21).

Sönmez et al. evaluated intoxication cases admitted to the emergency department within four years. In their study, drugs were found as the most used substance. However, methyl alcohol (33%) was found to be the deadliest substance (22). Drugs were found as the most used substance. However, methyl alcohol (33%) was found to be the most fatal substance (22).

Death cases due to methyl alcohol intoxication are very common in forensic medicine practice. However, if we look at the statistics, it is seen that deaths due to methanol intoxication have made periodic peaks in our region since 2016 (23,24). With the deaths that arise from methanol intoxication, many patients are disabled. All this indicates the necessity to bring the methanol intoxications that cause deaths and injuries to the agenda of the physicians.

2. Metabolism

Methanol is easily absorbed from the gastrointestinal tract, and then quickly distributed to body fluids. Methanol does not bind to plasma proteins. Methanol is slowly metabolized with alcohol dehydrogenase (ADH) at a ratio of 1/10 ethanol by 0 degree kinetics. The half-life detected depends on the methanol serum concentration (as the serum level increases, the half-life extends) and whether the metabolism is inhibited (by ethanol, fomepizole). It can vary between 2.5-87 hours. Only approximately 3% is excreted unchanged by the kidneys and less than 10-20% by inhalation (25).

Alcohols are sensitive to chemical or physical oxidation. Thus, alcohol dehydrogenase and aldehyde dehydrogenase, which oxidize alcohols to acids, are the main means of detoxification of ethanol and methanol. With the effects of alcohol dehydrogenase enzyme in the liver, methyl alcohol oxidizes formaldehyde, catalysts are NAD / NADH (26).

Ethanol is a competing substrate for alcohol dehydrogenase and greatly inhibits the metabolism of methanol to formaldehyde (27). Formaldehyde is 33 times more toxic than methanol. However, the formaldehyde cannot be detected in the blood due to the very short half-life (about 1-2 minutes). The return of formaldehyde to formic acid takes a very short time. Formic acid, which is six times more toxic than methanol, is excreted from the body by converting it into CO_2 and H_2O through enzymes bound to folate (10,26,28) (Figure 1). The half-life of endogenous formic acid is between 1.9-9.3 hours, and during dialysis, half-life may decrease up to 1.5-3.1 hours (25).

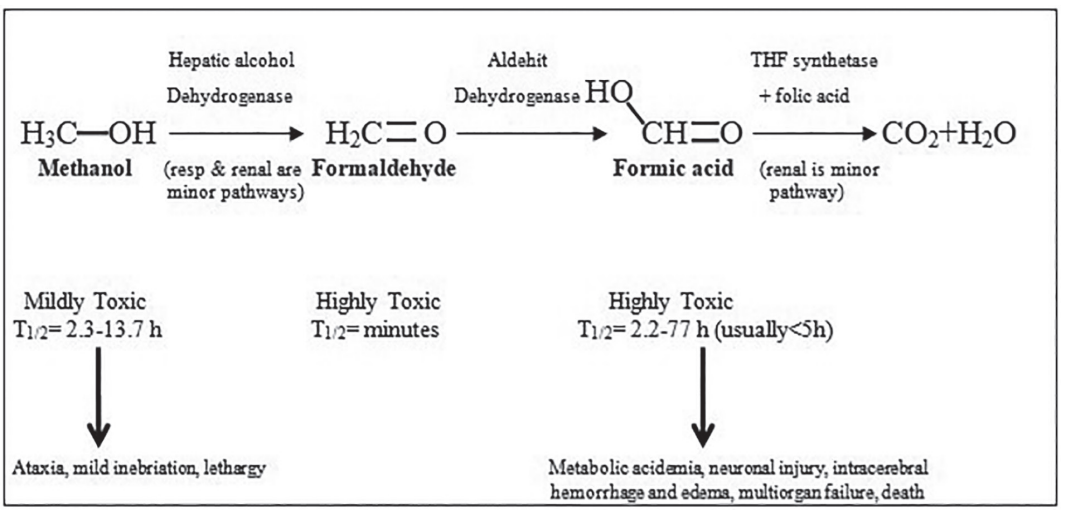

Figure 1. Metabolic biotransformation and clinical manifestations of methanol (28).

3. Intoxication

Methyl alcohol, which is added as a denaturing agent to ethyl alcohol, is the most common cause of intoxication. Alcoholic individuals' consumption of denatured alcohol products such as spirits as a liquor is an example of this (29).

Chronic alcoholics tend to drink anything that contains alcohol. Intoxication may develop as a result of using products containing methanol or consuming illegally prepared alcoholic beverages that should not contain methanol under normal conditions. In young individuals, intoxication may occur accidentally as a result of suicide or using methanol instead of ethanol (27).

Exposure to methyl alcohol steam or dermal exposure may cause intoxication in the industry. The workplace exposure limit (TLV-TWA) for inhalation recommended by ACGIH (Association Advancing Occupational and Environmental Health, USA) is 200 ppm on average over an 8-hour period, STEL: 250 ppm. The level (IDLH) reported to be urgently dangerous to human life and health is 6000 ppm (25,30-32). According to ACGIH data, the maximum permissible concentration for skin contact is 200 ppm (270 mg / m^3) (31-33).

Methyl alcohol may sometimes lead to epidemics. As a result, mass poisoning and mass death may occur (27, 34-36). The most known mass disaster in the world occurred in 1951 in Atlanta. 90-gallon illegal whiskey containing 35-40% methanol was consumed, resulting in 323 poisoning and 41 deaths (10,27,37). In our country, it was reported that 21 people died in 2004, 23 people died in 2005, 28 people died in 2015, and tens of people were hospitalized due to the methanol in fake raki consumed (23,38,39).

Kaya et al. reported that the deaths of 78 cases occurred due to methanol intoxication in the study in which the autopsies were performed retrospectively in Adana Forensic Medicine Institute from May 2016 to 2017 (24).

Methanol is easily and rapidly absorbed in the human body by all contact routes (skin, respiratory tract or gastrointestinal tract). Methanol passes through all membranes, so it is a liquid type that can be distributed evenly to all tissues and organs according to the amount of water. The normal blood concentration in the human body is 0.00015 g/dL or less. This is obtained from endogenous production and dietary sources. (3.40).

The fatal dose for humans has not been established with certainty. However, studies have shown that this rate may vary widely. The minimum fatal dose is reported to be approximately 100 ml (10). In various studies, the lethal dose of oral methanol is reported to be 30-240 ml (25.41), 1gr/kg (41), 300-1000mg/kg (42), 0.5 ml/kg (43). The minimum fatal concentration in the blood is 0.04 g/dL (3).

In Bennett et al.'s study, 323 cases, it was reported that fatal intoxication occurred after only 15 ml intake of 40% methanol (37), Ziegler reported in his study that when taking methyl alcohol pure, one teaspoon caused blindness and one ounce of death (44). On the other hand, in a reported case, oral intake of more than 500 ml of methanol did not cause death or blindness (10). Ocular morbidity is a well-known consequence of methanol poisoning. Cases of blindness have been reported after consumption of up to 4 ml (9,10).

According to an opinion, consuming in ethanol before consumption of methanol or consuming methanol and ethanol together may affect toxicity for a certain dose of methanol. It is also important whether the person has a folate deficiency. Thus, the width of the minimum toxic dose limit in the human body can also be explained (10,45).

As a result of intake of methanol with different exposure patterns, the highest methanol concentration can be found in blood, aqueous-vitreous humor and bile, brain, kidneys, lungs and spleen (40).

In fact, methanol itself is non-toxic, which may cause drunkenness, but it does not have cytotoxic properties. The main cause of toxicity is methanol metabolites (10). Methanol is first metabolized to formaldehyde and then to formic acid by dehydrogenation. Formaldehyde and formic acid are highly reactive, easily bound to tissue proteins, and leads to inhibition of the cytochrome oxidase system, which affects oxidative metabolism (10,46).

Most of the toxicity is thought to arise from formaldehyde. However, it has been reported that formic acid is more responsible for these effects. In studies of serum formic acid concentrations and methanol levels, it has been shown that formic acid concentration is more compatible with clinical findings (10). Studies have shown that ocular symptoms that arise from methanol poisoning can be reproduced in animal models by applying formic acid alone (40,47). Humans and primates are highly sensitive to methanol-induced neurotoxicity because their capacity to oxidize formic acid is limited (40).

At the beginning, formic acid cumulation may directly cause acidosis. There is a cytochrome oxidase complex at the far end of the respiratory chain in mitochondria, and as a result of its inhibition, "histotoxic hypoxia" occurs. Oxidative degrades in phosphorylation, causes accumulation of lactic acid, thereby deepening acidosis. Formic acid interacts with intracellular respiration and promotes anaerobic metabolism, thereby producing lactate. Increased lactate concentrations and tissue hypoxia,

lowers pH and causes further undissociated formic acid formation. Format and lactic acid, both of them, contribute to anion gap increase in methanol poisoning (48).

4. Clinic

The symptoms and signs of methanol poisoning are usually related to the central nervous system, eyes, and gastrointestinal tract. Most symptoms are associated with metabolic acidosis (10,25,48).

The clinic of methanol intoxication contains typically mild central nervous system depression followed by partial dose of methanol a latent time of approximately 12-24 hours. The conversion of methanol to formaldehyde is slow, which causes delay time. The fact remains that, this range can be quite variable and it can be less than an hour or up to 72 hours. If methanol is taken simultaneously with ethanol, the latent period is longer (10,25,48).

Acidosis is usually not seen, as it is not metabolized to toxic products in the first few hours after oral intake of methanol. A marked increase in osmolar space can be observed; an osmolar space of the 10 mOsm/L is correlated with the toxic concentrations of methanol (25).

After a latent period of up to 30 hours, severe anion gap can be detected with metabolic acidosis, visual disorders, blindness, seizures, coma, myoglobinuria, and acute renal failure and death. The primary toxic factor is metabolic acidosis in methyl alcohol intoxication. In this type of intoxication, drunkenness is not an important symptom (9).

Visual impairments are common and diverse. These disorders may lead to blackout, blurred vision, flash, photophobia, hemianopsia, visual disorder expressed as "seeing a snowstorm" of patients, or even to the total loss of light perception. It is reported that, in a large epidemic, some visual symptoms have been detected in all patients with mild acidosis and more than half of patients without acidosis. Abnormal pupil light reflexes; It has a wide range from a decreasing reaction to fixed and dilated pupils (10,25,49,50). Funduscopic examination may detect optic disc hyperemia or paleness, venous enlargement, peripapillary edema, and retinal or optic disc edema. Visual disorders may occur within 6 hours in conscious patients (25,49).

In mild-to-moderate methanol poisoning, headaches, drowsiness, abirritation and confusion can often be seen. Very little euphoria occurs compared to methanol ethanol. In severe cases of methanol poisoning, coma and contractions indicate the presence of brain edema. In addition to blindness, people who survive after severe methanol poisoning may develop a Parkinson's-like extrapyramidal syndrome characterized by rigidity, bradykinesia, mild tremor, mask face, abirritation and mild dementia. These clinical effects are generally associated with radiographic evidence of necrosis and sometimes hemorrhage in putamen and subcortical white matter. Some authors claim that these hemorrhages occur due to heparin used during dialysis; the fact remains that, it has been shown that putaminal hemorrhage develops in patients who have not received dialysis treatment. Rare neurological complications of severe methanol poisoning like transverse myelitis, cognitive deficit and pseudobulbar palsy may occur even without hypoxia and hypotension (17,48,51).

Methanol may typically cause nausea, vomiting and abdominal pain. Abdominal pain, which is a consequence of the development of pancreatitis, can be very severe. Nevertheless, the absence of gastrointestinal symptoms does not exclude serious toxicity. Acute pancreatitis, defined by high serum amylase, is a common complication of severe methanol poisoning, and pancreatitis has been confirmed in autopsy studies. The increase of the level of hepatic aminotransferases is generally mild and temporary (10,48).

Myoglobinuria is a rare complication of methanol poisoning. And also, the presence of myoglobinuria may cause kidney dysfunction (48,52).

Kussmaul breathing may be observed in cases with severe acidosis. Bad prognostic factors are bradycardia, shock, long-term coma, seizure, persistent acidosis and anuria. Deaths that occur during epidemia of methanol poisoning usually occur as a result of respiratory insufficiency and sudden respiratory arrest (10).

5. Laboratory Properties

a. Acid - base disorders

The presence of severe metabolic acidosis with increased anion gap and increased osmolar gap indicates strong methanol or ethylene glycol poisoning. Still, similar laboratory abnormalities can be detected in some clinical situations. Examples are diabetic ketoacidosis, alcoholic ketoacidosis, multiple organ failure, chronic kidney failure, and critical disease (10,48,50).

b. Osmolal gap (OG)

Osmolarity (osmol per liter solution) and osmolality (osmol per kilogram solvent) are measurements of the amount of particles solubilized in the solution. Osmolal gap is a quick estimate of unmetered osmotically active components in serum based on the difference between the measured osmolality and the calculated osmolarity. Osmolal gap is a rapid prediction of unmetered osmotically active components in serum based on the difference

between the measured osmolality and the calculated osmolarity. In the physiological state, there is an osmolal gap of approximately 10 mOsm/kg H_2O. Significant value for OG is greater than 10-15 mOsm/kg H_2O. Consuming methanol may cause significant osmolal cavity (OG) production. For every milligram of methanol per deciliter, OG increases by approximately 0.34 mOsm/kg. A methanol concentration (500 mg/L) of 50 mg/dL increases OG by 17 mOsm/kg H_2O. Methanol metabolites have little effect on OG. Because of that, the maximum OG occurs after the absorption of methanol before metabolism. While methanol metabolism progresses, OG decreases and anion gap increases. During methanol poisoning, OG usually exceeds 20 mOsm/kg H_2O, but OG may be normal at the end of the process. This is because toxic formic acid concentrations develop during methanol metabolism (48).

c. Hematological and biochemical abnormalities

Routine laboratory examinations required for the detection of severe toxicity are as follows: serum methanol and ethanol concentrations, serum electrolytes, serum calcium, complete blood count, serum blood urea nitrogen and creatinine, urine analysis, serum osmolarity, hepatic aminotransferase enzymes, serum amylase and serum creatine kinase (48.50). Factors that make it difficult to relate serum methanol concentrations to clinical effects include sample timing, individual variability, concentration of toxic metabolites, and ethanol intake (48.50).

Peak methanol concentrations below 20 mg/dL (200 mg/L) are generally asymptomatic. However, not to misinterpret the methanol concentration, the time elapsed since consumption, taking with ethanol and acid base status should be considered. Peak methanol concentrations above 50 mg/dL (500 mg/L) indicate severe poisoning, especially if there is an increased anion-gated metabolic acidosis (48,52).

Co-consumption with ethanol reduces the toxicity associated with a certain concentration of methanol. It delays the expression of signs and symptoms correlated with methanol exposure (48.53).

6. Treatment

General precautions should be taken to ensure airway patency, sufficient ventilation and sufficient systemic perfusion, as in the first intervention management for all empoisoned patients. Gastric lavage can be recommended as a traditional method to removing poison residues, but it is useful only when administered immediately after intake, as methanol is absorbed very fast from the gastrointestinal tract (10).

The medication of an antidote in therapy, which blocks the function of alcohol dehydrogenase and thus prevents the formation of toxic metabolites, is the basis of treatment for methanol intoxication. In addition, metabolic acidosis and electrolyte abnormalities may need to be treated. Hemodialysis may also be required. There are two antidotes that block the ADH metabolism used today: ethanol, a competitive ADH substrate, and Fomepizole, a competitive ADH inhibitor (28.54).

Ethanol is a traditional antidote for the treatment of acute methanol poisoning. It has about ten times more affinity for alcohol dehydrogenase than methanol. Ethanol effectively inhibits the conversion of methanol to formaldehyde when the blood serum concentration rises above about 22 mmol. Another effective antidote is fomepizole (4-methylpyrazole). It has several times more affinity for ADH than methanol (39.45). Fomepizole was recently included in the WHO List of Essential Medicines (2013). However, drug supply is limited (29,45,55). Fomepizole is used as an antidote in place of ethanol in many places in the United States (29.55).

Ethanol is a substrate for ADH, fomepizole (4-methylpyrazole) competitively inhibits the ADH enzyme and blocks metabolite formation. (Figure 2) The adverse effects of high doses of ethanol do not result in the treatment of fomepizole. Thus, it is the preferred antidote in severe poisoning (56).

Some reasons to prefer fomepizole as an antidote rather than ethanol are higher affinity for ADH than ethanol, minimal side effects, no necessary to check fomepizole blood levels, no hospitalization in the intensive care unit (29.55).

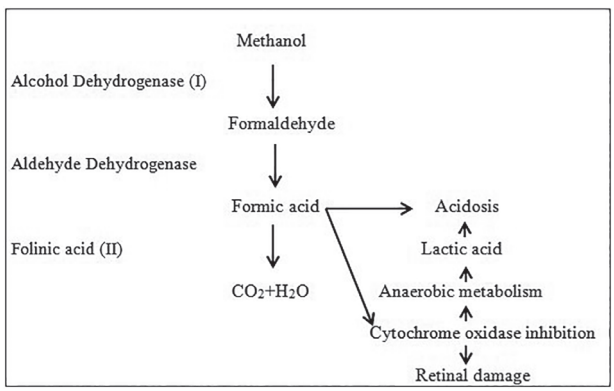

Figure 2. Elimination of the harmful effects of methanol by antidotes: (I) ethanol and fomepizole inhibit both methanol metabolism and the formation of toxic metabolites. This treatment approach is very important. (II) Folinic acid may increase formic acid metabolism; still, in daily clinical practice, this effect is much less important than in (I) (56).

Indications for using antidote treatment using fomepizole or ethanol, in cases of diagnosed or suspected methanol intoxication are; ≥20 mg/dl plasma methanol concentration (6.2 mmol per liter), an osmolal gap of >10 mOsm/L per liter with toxic methanol consumption, arterial pH level <7.3 with suspicion pf methanol poisoning, serum carbon dioxide level <20 mmol/L, osmolal gap >10 mOsm/L. At least two of these indications are required (29,48,55).

The clinical purpose of ethanol therapy is to achieve a therapeutic serum ethanol level between 100-150 mg/dl. Recommended doses of ethanol for methanol poisoning are 0.6-1 g/kg intravenously as maximal tolerable dose (7.5-12.5 ml ethanol/kg in 10% glucose solution) or oral 40% ethanol solution (2.5 ml/kg) (29.48.55).

For the patients who do not receive hemodialysis treatment, fomepizole's maximale tolerable dose of is 15mg/kg and maintenance dose 10mg/kg are administered every 12 hours. They should be used in 30 ml infusion in 100 ml of 0.9% NaCl or 5% dextrose. Fomepizole induces its own metabolism, so after the 48th hour of treatment, the dose is increased to 15 mg/kg. The drug doses administered to the patients who received hemodialysis treatment and who did not are the same. Only, the drug should be administered to the patients receiving hemodialysis treatment six hours after the first dose and then every four hours, too (29,48,55).

Hemodialysis eliminates methanol and toxic metabolite formic acid in the blood. In general, dialysis treatment should be started regardless of symptoms in all cases with ocular symptoms and developing kidney failure. Indications for hemodialysis are 50 mg/dL (15.6 mmol/k) or more serum methanol concentration, presence of metabolic acidosis, seizures, coma and visual disorders (27,28,48).

According to guidelines based on clinical experience rather than evidences, treatment should be continued until the plasma methanol concentration falls below 20 mg per deciliter (6.2 mmol methanol per liter). The exact point to stop the treatment of the patient has not been reported, still, it has been reported that it is safe to stop treatment when the plasma methanol concentration is 25-30 mg per deciliter (9.4 mmol methanol per liter) (29.48).

The described relationship between formic acid metabolism and folic acid-dependent enzyme systems shows that, folic acid can play a therapeutic additive in methanol intoxication. Thus, folic or folinic acid should be administered intravenously every four hours (50-100 mg) to all patients diagnosed or suspected with methanol poisoning (10,48). Also, this is may be necessary that to include very high amounts of bicarbonate ($NaHCO_3$) into the treatment to reach normal pH values (9,48).

7. Prognosis

Methanol poisoning has a quite high mortality ratio. The degree of metabolic acidosis at the first admission (low serum bicarbonate, high anion gap, serum lactate and format concentrations), negative serum ethanol, lack of respiratory compensation when severe acidotic and coma are bad prognostic factors (45).

The time from the first application to a hospital to the diagnosis is very important. There is no consistent coherence between serum methanol concentration at the first application and mortality, but patients with bad results frequently have a higher serum methanol concentration. Stress-induced hyperglycemia in the worsened patients has been claimed as a bad prognostic factor (45).

In the 2007 study of Hassanian-Moghaddam et al., it was reported that the mortality rate was 90% in patients with comatose state at the time of admission, 20% in non-comatose patients, and there was a significant difference in mean pH in the first arterial blood gas values of the deceased patients and survivors (57).

In another study, it was reported that untreated methanol intoxication was associated with a 28% mortality rate and 30% vision deficiency or blindness in survivors (29).

In the study of 725 cases by McNally, it was reported that, 90 cases experienced total blindness, 85 cases had visual defect at some degrees during acute poisoning, 335 people survived. Among the survivors, visual impairment recovery is common (10).

In the epidemic reported by Chew et al., there were 26 people, all of whom were somewhat acidic and 15 had visual impairments in the acute phase, but only two patients had permanent vision loss (58).

The mortality rate is higher in the individuals who survive methanol intoxication in the next six months compared to the normal population (59).

8. Postmortem Findings

a. Macroscopic and histopathological findings

In patients who died due to methanol intoxication, internal and external postmortem findings and anoxia/hypoxia findings are similar in macroscopic examination. In cases, cerebral edema and congestion, intracerebral hemorrhage, pulmonary edema, erosion and hemorrhage in the gastric mucosa can be detected. Cases of subendocardial bleeding are rarely shown. Changes due to chronic alcoholism such as hepatosteatosis, micronodular, macronodular and mixed type cirrhosis are observed in the liver (25,60).

Common histopathological features observed are cerebral congestion and edema, basal ganglion hemorrhage, basal ganglion necrosis. In histology, capillary obstruction in the putamen, hyperemia and hemorrhagic necrosis of the putamen can be detected. Bleeding can be detected in the tissue surrounding the optic nerve. Common histopathological features observed; cerebral congestion and edema are basal ganglion hemorrhage, basal ganglion necrosis, capillary obstruction in the putamen in histology, hyperemia and hemorrhagic necrosis of the putamen. Bleeding can be detected in the tissue surrounding the optic nerve. Alveolar edema and hemorrhages in the lungs, microvesicular and macrovesicular fatty changes in the liver, glomerulosclerosis, tubular degeneration, hydropic changes and interstitial bleeding in the kidneys may occur (20,27,60,61).

In Japan, Mittal et al. published a study on 28 cases that resulted in death. It was reported that, in 85.7% of cases, neuron contraction and degeneration in the parietal cortex. Putamen degeneration and necrosis (7.14%), hemorrhage in optic chiasm (3.5%) and spongy degeneration (7.14%) were also detected in the same study. Severe renal tubular degeneration and patchy necrosis have been reported in all cases (62).

b. Collection, preservation and transportation of postmortem laboratory samples

In cases of methanol intoxication, external pathognomonic findings cannot be detected except non-specific autopsy findings. Because of that, the most important step in the diagnostic process is toxicological examinations. Proper samples should be collected with proper methods and in proper quantities, stored and transport to the laboratory properly. The ideal postmortem blood sample to be used in forensic toxicological analysis should be taken from the femoral or jugular vein area and the sample should have sufficient amount (approximately 10-30 mL). In condition of putrefaction and blood samples deterioration, it is recommended that vitreous fluid should be used for alcohol determination. Blood samples should be collected in clean and capped tubes with protective materials, such as NaN_3, NaF at a rate of 0.5-2% (w/v), labeled. The name, age, gender, type of the sample, date and time of collection should be written on the label. The safety chain should be followed until the samples collected during the autopsy are delivered to the laboratory. Preservation and transportation should be carried out in accordance with cold chain rules. Ideally, samples should be delivered to the laboratory immediately after collecting and toxicological analysis should be carried out. Sometimes, the sample may need to wait a while until analysis. In this situation, antemortem or postmortem samples should be stored at 4°C if analyzed within a few days. If it waits longer, it should be stored at (-20)-(-80) °C (20,63-65).

c. Postmortem laboratory findings

While methanol intoxication in humans, blood methanol and formic acid concentrations are quite variable, various studies of postmortem methyl alcohol levels are in the range of 74-485 mg/dl (20), in the range of 55-479 mg/dl (66), in the range of 151-300 mg/dl (18), in the range of 18.2-465 mg/dl (24), in the range of 50-755 mg/100 ml (67) and in the range of 0-826 mg/100 ml (23).

In Mittal et al.'s studies, they reported that the levels of methanol in the blood and internal organs were variable, the average level of methyl alcohol was 155.87 mg (maximum 420.4 mg), and no alcohol was detected in the blood of seven cases. However in all these situations, they reported that they revealed the presence of methyl alcohol in viscera and stomach contents (62).

Many factors can be claimed as a reason for the variation of the half-life in such a wide range, such as the volume and percentage of methanol consumed, the duration of survival, whether medical intervention was performed, consumption of ethanol simultaneously, time between death and alcohol consumption, material intake, and time to analyze (20,68,69).

If death occurs without medical intervention, postmortem methanol and formic acid levels are high enough to explain death. If death occurs despite medical intervention, postmortem methanol and formic acid levels can be found below the lethal dose. In such cases, the analysis of antemortem samples considerably contributes to the interpretation of the results obtained. For easy interpretation of analytical results, it is important to learn a complete case history including information on medical intervention techniques used and survival time. In case of overdose of methanol consumption that causes death of individuals, postmortem methanol and formic acid concentrations are adequate to explain the cause of death (69).

Hospitalized patients who received hemodialysis treatment, it was reported that when the postmortem methanol levels were compared, the brainstem methanol level was very high compared to the blood. Hemodialysis effectively reduces toxic blood methanol concentrations. Thus, brain methanol concentrations can be many times more than blood levels. Therefore, in addition to blood analysis of patients with longer survival time, brain methanol analysis is recommended after autopsy (68).

In cases with a significant time gap between methanol consumption and death and negative methanol in the blood, methanol intoxication can be confirmed by determining formic acid in vitreous humor or blood samples (70).

9. Conclusion

In our country, the majority of the cases of autopsy and methanol poisoning in recent years consist of distillers or people who consume fake alcoholic products that are known to be cheaper. It is observed that retails of fake alcohol (no record label), as well as the amount of distillers have increased with the escalation of alcohol prices. In addition to licensed ethanol distributors, illegal supply of methanol to the market leads to an increase in the amount of methanol poisoning cases, too. That is why, consumption of uncontrolled/ illegal products and methanol poisoning can be prevented through an effective inspection mechanism over chemicals in question.

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