



Review Article

Methanol Formation, Toxicity and its Impact on the Human Nervous System and Liver

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ABSTRACT

Methanol poisoning is a severe public health issue that causes disease and death, particularly in developing countries. Exposure can occur intentionally or unintentionally through several industrial products such as cleansers, solvents, antifreeze, perfumes, and paints. The toxic dose of methanol is approximately 1g/kg, emphasizing its potent toxicity. Methanol intoxication is chiefly caused by the harmful metabolites which are formed during its breakdown. These metabolites encourage metabolic acidosis. Formic acid, a methanol breakdown product, troubles mitochondria, distressing cytochrome oxidase and ATP production. Methanol-related problems include neurological disorders, vision problems, liver impact, Alzheimer's, and Parkinson's. Key lab tests, including osmolality and anionic gap, aid in recognizing alcohol harm. Furthermore, detecting a faint smell of methanol in the breath, observing visual disturbances, and altered sensory neurons, seeing a history of abdominal pain, and conducting routine checkups support the early diagnosis of methanol poisoning. Treatment using prompt gastric lavage, sodium bicarbonate given intravenously, management with ethanol, folate-dependent folate systems suggest, dialysis, competent ADH inhibitor "pyrazole", specific antidote "Fomepizole" can be used to treat methanol poisoning. Regular toxicologist check-ups are critical in such cases. Definite symptoms like basal ganglia issues and eye problems require consultations with neurologists and ophthalmologists. For cases needing hemodialysis or liver tissue recovery, consulting a nephrologist is essential. It is suggested to immediately act to prevent harm, especially for industrial workers, rural alcohol sellers, those with alcoholism, and vulnerable youth vulnerable to methanol poisoning.

INTRODUCTION

Toxic alcohol is collectively used for various alcohols including methanol, isopropanol, ethylene glycol, etc. Methanol is one of the deadly poisoning alcohols found in various substances ranging from daily use chemicals to industrial use chemicals. Methanol toxicity is one of the threatening issues of illness and death in emerging and unindustrialized countries worldwide [1]. Methanol is a volatile, and colorless fluid with little odor that can be

manufactured on an industrial scale when carbon monoxide or dioxide reacts with hydrogen by catalytic reaction [2]. The objectives of the study include reviewing the literature on methanol formation, poisoning, its impact on the nervous system and liver, and the possible feasible treatment for alleviating toxicity and death rates. Methanol is the main constituent of many illegal beverages, cleansers, solvents, antifreeze, perfumes and paints.

Methanol-containing beverages known as denatured alcohol are unsuitable for drinking [3]. Poisoning is due to the transformation of methanol to formic acid and formaldehyde [3]. Formic acid induces severe metabolic acidosis that results in mortality [4].

Signs and Symptoms

Studies and academic publications [5] provide the finest summaries of methanol toxicity in individuals. The signs and symptoms are (i) A short-lived but milder depression of the central nervous system than observed after ethanol ingestion [6]. (ii) A dormant phase of 12-24 hours without symptoms after ingesting alcohol in the absence of signs or symptoms [7]. (iii) Following the dormant phase, serious metabolic acidosis takes place [8]. (iv) The characteristic complaints of ocular toxicity are described as followed by blindness, coma, other CNS signs and death [9].

Acute and Chronic impact on Humans

Noxiousness from formic acid in methanol primes to acidosis, neurological disorders, blindness, and can be deadly [10]. Concern for methanol toxicity has rarely involved the chronic effect of long-term or occupational exposure, despite some historical examples of chronic exposure leading to disease-like symptoms, such as those related to multiple sclerosis [11]. Explicitly, research has exposed raised levels of the methanol formaldehyde metabolite in the urine, plasma, and cerebrospinal fluid of individuals identified with Alzheimer's disease (AD). Additionally, this metabolite was observed to be increased in the hippocampus of the brain during postmortem studies on individuals with Alzheimer's disease [12]. The basal ganglia are also affected by methanol. In case of severe poisoning, hemorrhagic and non-hemorrhagic damage in the putamen are common problems. Individuals can experience Parkinsonism or additional dystonic/hypokinetic diagnostic symptoms as a consequence of this damage [13]. Seldom, methanol intoxication reasons Parkinsonism via mitochondrial injury and ATP exhaustion [14].

Populations at risk

Attempts to commit suicide with methanol are rare [15]. Although, accidental methanol toxicity can happen in a number of situations and in several distinct demographics, such as communities of developing nations: Methanol is frequently used in "alcohol smuggling," which takes place in remote regions, in a number of these nations. Since it is inexpensive, people from poorer social groups frequently consume it [16]. Unintentional overdoses in kids have been seen. Methanol is frequently present in easily accessible products like antifreeze, fragrances, thinners, photocopy fluids, and washing fluids [17]. Alcoholics frequently replace methanol with ethanol. Employees in the industrial sector face exposure to methanol emissions in a factory

setting. In addition to being employed as an extractor in biochemical reactions as well as a denaturing reagent in alcohol, methanol is additionally utilized in the manufacturing of formaldehyde and the manufacturing of lacquers [3].

Toxicity

Methanol lethal dose estimation is near 1g/kg. Methanol toxicity might occur mistakenly or deliberately (suicide, abuse or misuse) [18]. Commonalities can be seen in the metabolism of both methanol as well as ethanol. Both alcoholic beverages release free oxygen radicals during metabolic reactions, which could also harm the liver [19]. A fatal type of poisoning, methanol poisoning could lead to serious metabolic acidosis, cognitive deficits, and vision problems. Ganglion cells, subcortical white matter, and hemorrhagic necrosis are the most common types of cerebral lesions associated with methanol poisoning [20]. Methanol is recognized as a human sedative. Moreover, both humans and lower species of rats are found to be vulnerable to methanol toxicity [21]. It is crucial to understand factors affecting methanol susceptibility, considering its toxicity process [22].

Route of exposure

The most important occupational exposure routes for the entry of toxic compounds are Inhalation and skin absorption. The respiratory system is readily absorbed by Methanol. Like other solvents absorption rate for liquid methanol is the same through the skin [23]. The amount of methanol retained in the body after inhalation is influenced by various factors, such as the concentration and duration of exposure, as well as individual physiological differences like metabolic rate. Other factors like respiratory ventilation and protective equipment may also affect retention. To ensure accurate and reliable information about methanol exposure, it is important to rely on evidence-based sources. Ingested methanolic acid is almost completely absorbed, as in the case of an accident and poisoning [24]. Alcoholic compounds are distributed in the body's water compartment.

Lethal dose

Although the exact lethal dose (LD) for individuals is unknown, the data points to a broad spectrum of possible values. Although the lowest deadly dosage is sometimes reported to be around 100 ml, it is said that 15 ml of 40% methanol causes severe toxicity when consumed [13]. Even though the quantity of concentrated relies on a variety of parameters, such as the individual's rate of metabolism, age and health status methanol poisoning can happen following ingesting as little as 10 mL of it [25].

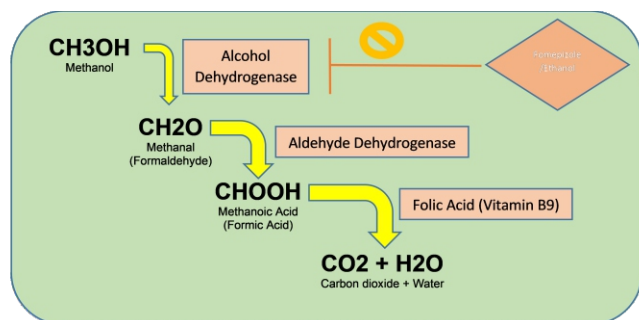
Methanol metabolism

On its own, methanol is a relatively non-toxic substance. However, it is considered to be a cytotoxic substance in

some circumstances and has been known to cause cellular damage [26]. Methanol metabolites, particularly formic acid, can cause cytotoxicity through inhibition of key metabolic pathways and accumulation of reactive oxygen species (ROS) in cells [27]. Several types of cells, particularly photoreceptors, hepatocytes, and neurons, have shown signs of methanol-induced mortality. Methanol-induced cytotoxicity has also been linked to mitochondrial dysfunction, leading to decreased ATP production and increased ROS production [28]. Dehydrogenation of methanol results in the formation of formalin and ultimately methanolic acid Fig. 1. The compounds are recognized as preventing oxidative degradation by blocking the cytochrome oxidase pathway, are highly reactive and are readily attached to the tissue's proteins [29]. While formalin has historically been associated with the majority of methanol-associated cytotoxicity, it appears that acidosis is more likely to be the cause of this condition. The visual symptoms of methanol intoxication could be reproduced in animal studies by administering a single dose [30]. The initial phase of the process of methanol oxidation is the production of formaldehyde (Figure 1).

Figure 1: Methanol breakdown mechanism

Cellular respiration is blocked by formic acid and takes part in metabolic acidosis [31]. Untreated metabolic acidosis can be lethal and might lead to blindness. Early interference can prevent death, but blindness can still occur. Understanding the time-toxicity link is vital for methanol toxicity knowledge [32].



Impacts / Effects

Although symptoms are frequently experienced, nausea, vomiting, and stomach pain are not always present. Epigastric pains may be quite painful and come with stiffness in the abdominal muscles [33]. Methanol intoxication can lead to definite brain lesions, distressing the basal ganglia and white subcortical areas, especially the bilateral putamina [34]. Initial signs of methanol poisoning comprise vomiting, nausea, stomach discomfort, fatigue, headaches, and disorientation. Later signs manifest as nervous system effects (coma, seizures, fatality), vision problems (blindness, optic degeneration, central scotomas, light flashes), and metabolic acidosis

with substantial anionic deficit. Optic nerve atrophy happens due to demyelination produced by formic acid inhibition of mitochondrial ATP production [34].

Acute and chronic impact on the nervous system

There can be hemorrhages as well as the central nervous system becoming inflamed and swollen in severe methanol toxicity [13]. Writers' highpoint methanol intoxication triggering bilateral putaminal microscopic hemorrhage in humans and animals. Survivors past 24 hours display distinct necrotic areas and variable severity of putamen hemorrhages, marking critical symptom [35]. Certain individuals, particularly those who exhibit a lengthy rate of survival following serious methanol toxicity, also exhibit ischemic alterations in the neurons of the hippocampal region, cystic necrosis of the cerebral white matter, and laminar necrosis of the cerebrum [36]. In a Japanese postmortem study (28 cases), 85.7% presented parietal lobe neurodegeneration and hemorrhage necrosis. Putamen is chiefly vulnerable to acidity in the nervous system. Higher methanolic acid levels in the caudate nucleus advise it as a primary site for necrosis in methanol toxicity [37]. In the case report, life expectancy spanned between a few hours to 10 days and comparable life expectancies were seen in several instances. Thus, it makes sense that there are not any notable disparities among the structural alterations within the brain [38].

Impact on liver and tissue

Methanol intoxication is a chief issue in Iran, producing liver toxicity symptoms. A study on 44 lethal cases exposed histological liver abnormalities, including steatosis, hepatocellular necrosis, and biliary stasis. The most common cases (86.36%) were men. Particularly, methanol concentrations above $127 + 38.9$ mg correlate with severe histopathological changes in hepatic tissues [38]. In contrast to such restrictions, just 3 instances of deadly methanol toxicity on the hepatocytes were discovered in Denmark over 6 years [39]. Men were 3.8 times more likely than women to die from methanol toxicity, and the majority of casualties were children [40]. Methanol toxicity reparations multiple organs. Cerebral CT shows putaminal hypodense lesions and hemorrhage. Methanol intermediates can encourage hepatic impairment through membrane dysfunction [41]. Research from the past indicates that ethanol causes hepatic damage. Initially identified steatosis, edema, and necrosis as indicators of liver disease. One investigation found that hepatic disease was caused by oxidative stress [42]. Given the commonalities between ethanol and methanol's chemical composition and metabolic channels, one might assume that methanol breakdown produces free radicals [43].

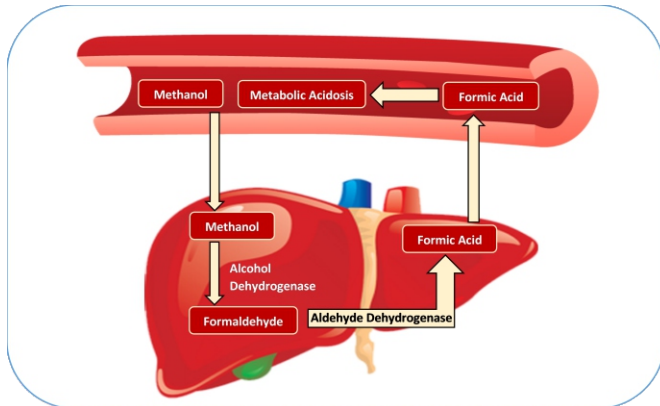


Figure 2: Methanol breakdown and metabolic acidosis

Laboratory findings and diagnosis

The severity of metabolic acidosis can broadly vary and is not strictly associated with the amount of methanol consumed. Both in animal trials and instances of human methanol toxicity, an increase in blood formate levels often overlaps with a decrease in blood bicarbonates, indicating that the acidosis is primarily caused by formate production during methanol metabolism [44]. There is occasionally a concurrent component of lactic acidosis. Furthermore, intracellular respiration can be affected by formic acid promoting lactate formation and anaerobic metabolism. However, an increase in lactate production causes side circulatory convulsion in many cases [45]. Clinical chemistry facilities' blood electrolyte profiling in their most basic version contains measurements of chloride, sodium, and CO₂. Anionic deficit or unexplained anion plasma level is characterized as:

$$\text{Anion gap} = (\text{Sodium}) - (\text{Chloride}) - (\text{CO}_2 \text{ content})$$

Acidosis and the formation of anionic components in the event of methanol toxicity are mostly caused by the development of formic acid and, less frequently, lactic acid. The anion deficit is a crucial potential diagnosing marker of methanol toxicity because of its easy accessibility and ease of use [46]. The blood osmolal gap, which is obtained from the difference between the actual and estimated blood osmolality in methanol scientific tests, is an additional significant marker. The equation $2(\text{Na}+\text{K})+\text{glucose}+\text{urea}$ may be utilized to measure plasma osmolality, exhibiting a typical value of 280–300 mOsm/kg

$$\text{Estimated osmolality} = 2 + \text{BUN sodium} / \text{glucose} + 2.8 / 18$$

$$\text{Osmolal gap} = \text{measured osmolality} - \text{calculated osmolality}$$

This difference explains other constituents of the osmotically normally present serum. Every exogenous solute inside the plasma triggers a rise in the osmolal gap. The molecular mass and molarity of the toxin in the blood are related to the osmotic action of a consumed toxin. The osmolal difference could expressly rise when methanol is

present because of its low molecular mass and medical toxicity is typically linked to reasonably high moles of alcohol levels. Nevertheless, ethanol intoxication remains the most frequent reason for an osmolality rise [47]. Therefore, the serum concentration of ethanol should be evaluated regularly when the osmolal gap is evaluated. Determining the quantifiable input of ethanol towards the osmolal gap is crucial since the difference could be significantly enlarged when there's ethanol inside the blood. This may be accomplished by adding an ethanol component to the osmolality calculation:

$$\text{Osmolality} = 2*(\text{Na}) + \text{Glucose (mg/dL)}/18 + \text{EtOH (mg/dL)}/4.6 + \text{BUN (mg/dL)}/2.8$$

The difference grows as a result of methanol or another unidentified material. osmolal gaps can be increased by some ingested toxins like ethylene glycol and isopropanol. When a person delivers a thorough consumption history, the prognosis is typically clear. Still, when they can't or won't, or if the signs are unclear, the prognosis becomes challenging. Methanol often has a subtle smell, not always obvious. Reports propose a formaldehyde odor in the breath or urine of methanol-intoxicated individuals. Stomach ache, though common, isn't a reliable indicator. Visual irregularities are the main physiological signs. Analytical tests revealing metabolic acidosis and raised anionic and osmotic gaps are highly valued for identification [48]. The primary toxicology-detecting batteries employed by clinical chemistry labs, that frequently employ liquid as well as gas chromatography, frequently contain methanol. The implementation of specialized therapy at the start of the program is probably going to lower the incidence and fatality [49]. This advice might be disregarded if the practitioner is confident that the institution's toxicological laboratories could provide such standard findings in a brief amount of time. The physician must establish a preliminary assessment according to the provided physiological findings if this is not feasible (Faint smell of methanol in the breath visual disturbance, altered sensory neurons, abdominal pain) history, and routine Laboratory results (High space osmol gap, high anionic gap, positive dosage of serum methanol, metabolic acidosis).

Distribution worldwide

Ingesting methanol, whether accidental or intentional, can cause noxiousness. Notably, a main outbreak in Atlanta stemmed from illicit whisky with 35–40% methanol, resulting in 323 cases and 41 deaths over 5 days [50]. It is extensively used in several industries and easily obtained in Iran. Due to religious rules and regulations consumption of alcohol is banned. For these reasons, the production of illicit less processed drinks having methanol in laboratories has grown in various parts of Iran [51]. In recent years, an

outbreak of methanol poisoning occurred in Iran where 972 cases were identified, including 706 deaths [52]. The toxicity of methanol has been well-established for over a century, and yet methanol poisoning continues to occur worldwide. Ingestion of adulterated alcohol is a common cause of methanol poisoning, particularly in developing countries [53].

Management

Steps should be taken to ensure proper breathing and perfusion for poisoned individuals. Use gastric lavage cautiously post-alcohol ingestion. Avoid ipecac syrup if consciousness is altered post-vomiting. Evidence for activated charcoal's efficacy is lacking [54]. Individuals who have serious metabolic acidosis who have been poisoned with methanol must be supplied sodium bicarbonate intravenously. According to studies, this treatment may theoretically restore visual symptoms, enhance sensory organs, and maybe decrease mortality [53]. The control of ethanol is the foundation of methanol toxicity treatments. As a result, both types of alcohol function as competitors. These enzymes do, nevertheless, very partially metabolize methanol compared to ethanol. It is critical to begin ethanol treatment for individuals having a documented record of methanol intake and for individuals suspected of methanol toxicity [55]. The relationship between the metabolism of formic acid and folate-dependent folate systems suggests that folic acid can play a role as a therapeutic complement. The methanol poisoning sensitivity increases in folate deficiency conditions. Folate administration raises the metabolism rate formed in methanol poisoning the toxicity of methanol poisoning is reversed by folate even when the vitamin is administered 10 hours after methanol dosing [56]. Alternatively, with the start of hemodialysis, the half-life of methanol was decreased from 8 to 2.5 hours. Since hemodialysis provides quicker clearing than peritoneal dialysis. Since hemoperfusion columns could quickly become saturated with methanol, they shouldn't be employed [57]. Pyrazole's harmful implications on the tissues and hepatic cells have limited its application as a possible treatment for methanol toxicity. Alternatively, 4-methyl pyrazole appears to be a considerably less harmful blocker of alcohol dehydrogenase. Although the medicine was employed in research, it has yet to be approved for medical usage within the US [58]. Treat methanol poisoning can be carried out by obstructing alcohol dehydrogenase with Fomepizole, followed by hemodialysis with sodium bicarbonate to correct metabolic acidosis and eliminate toxins. Priority is continuous renal replacement therapy (CRRT) [59]. Treating methanol intoxication includes the administration of ethanol to block the production of folic acid and formate to improve the

oxidation to carbon dioxide. Dialysis should be continued for a long period to completely remove formic acid. Cell mechanism of proton excretion that is comparable to cyanide poisoning [60]. An anionic exchange inhibitor drug for example, furosemide, may be a potential benefit, the Nonionic diffusion gradient of formic acid can be reversed favoring the excretion of formic acid rather than reabsorbed [61]. If a physician wants to check the exposure to alcoholic compounds simple steps are followed. First, if someone ingests methanol or alcoholic compounds the symptoms of organ damage occur within a specified time e.g., vision blur, and kidney and liver tissue damage. But if the intake is not sure by the person, then you will have to use other techniques like monitoring or evaluation via alternate diagnostic approaches for alcohol ingestion, inhalation or absorption [62]. If signs are observed, use fomepizole to treat the ADH blockade, contact a nephrologist, and consider hemodialysis [63], but if symptoms are not clear so question arises how much amount of ethanol is used to overcome the damage is ethanol >20 mg / dL [64]. On the other hand, if ethanol is more than 20 mg / dL use Trend Ethanol until <20 mg/dL, then proceed to Block A if not use Trend $[HCO_3^-]$ Q2-4H for 12 hours [65]. ADH blocking therapy must be initiated in an individual suspected of consuming harmful levels of methanol to show a lowering osmolar difference with a rising anion gap (related to HCO_3^- ions).

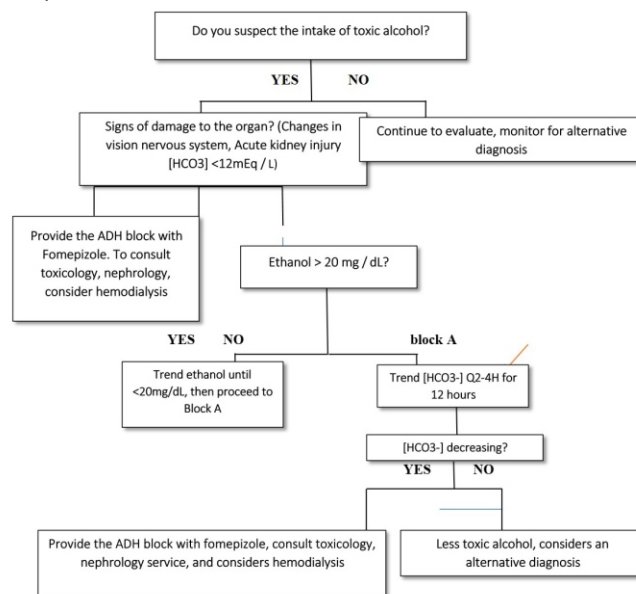


Figure 3: Flowchart representing the standard screening and treatment measures for managing the harmful effects of methanol toxicity

CONCLUSIONS

Methanol outbreaks constitute a significant issue and have a negative impact on vulnerable communities. Acute

methanol poisoning is a potentially disastrous public health hazard that can result in high mortality. This is typically owing to a significant number of profoundly intoxicated patients, along with a lack of understanding of methanolic poisoning, insufficient treatment choices, and diagnostic limitations. Associations between NGOs, local authorities, and international experts can significantly improve consequences in resource-constrained situations. However, complete reports on these epidemics are presently inadequate. Advocacy efforts are vital to certify the presence of fomepizole in the list of critical treatments, supporting the importance of addressing methanol poisoning efficiently. Prioritize referring a specialized toxicologist or the nearest poison control unit as a first step. Involve a toxicologist to team up with a nephrologist if dialysis or hepatocyte recovery is deemed compulsory. Pursue supervision from a neurologist if symptoms suggestive of basal ganglia involvement are present. Refer an ophthalmologist promptly if ocular symptoms are detected.

Authors Contribution

Conceptualization: MA

Methodology: MA, MMA

Formal analysis: HK, SHK

Writing, review and editing: MA, MMA, HK, WN, KS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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