CHAPTER 2

METHANOL POISONING

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INTRODUCTION

Methanol (CH3OH) is among the toxic alcohols used as industrial agents and house holds. Historically it has been obtained from the distillation of wood and hence, it is also termed as wood alcohol (1). In 1923, methanol has been introduction as an industrial agents and found usage area in a wide spectrum including airplane fuel, photocopy machines, dry gas, perfumery etc. Methanol poisoning (MP) can occurs with accidental or intentional exposure to methyl alcohol and causes significant morbidity and mortality.

Although methanol itself is not toxic, its metabolites are highly toxic agents. It is metabolizes to formaldehyde and subsequently to formic acid. (Biotransformation of methyl alcohol is shown in Figure 1. Both formaldehyde and formic acid are responsible for MP that can lead to hemodynamic instability, blindness, and mortality. MP can cause severe cellular dysfunction mainly due to accumulation of organic acids including formic acid and their anions produced by its metabolism. MP is more common especially in certain developing and underdeveloped countries where alcohol taxes are high or alcohol sell is banned due to religious reasons. However, MP cases may also be seen in the developed countries. In illegal alcohol production in these countries, methanol is used as a substitute of ethanol, which is more expensive to produce beverages, leading to MP. This chapter begings with etiology, epidemiology and pathophysiology of MP. Diagnosis, manaegment, prognosis and complications of MP are also addressed in the light of the current literature.

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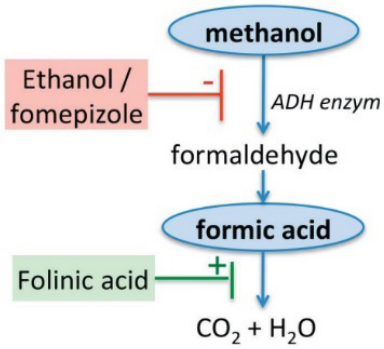

Figure 1. Biotransformation of methyl alcohol

ETIOLOGY

Methanol poisoning (MP) is a clinical condition that leads to multiple organ failure and mortality. Accidental or intentional methanol poisoning occurs upon inhalation, ingestion or dermal absorption of methanol. The most common form of MP is oral ingestion of illicit or adulterated liqours. It is used as a substitute of more expensive ethyl alcohol (ethanol) by alcohol abusers, especially in socioeconomically underdeveloped countries (2), because when methanol is taken orally, it is absorbed as ethanol or ethyl alcohol by the gastrointestinal system (3). MP is more commonly seen in countries where alcohol sell is banned or alcohol tex are high, resulting in illegal alcohol production using methanol. MP is also seen as a form of suicidal attempts with oral intake of various substances containing methyl alcohol such as cologne, perfumes, windshield water fluid, shoe dye etc. (4).

Herbal beverages contain some level of methanol and alcohol impurity. The factors affecting amount of methanol and ethanol in herbal waters include macerating and bginning of distillation process, temperature, wood contentf of the plant, storage of aromatic substances and pasteurization of distillates (5). Passing time increase the level of methil alcohol in these beverages. A study from Iran showed that more than 50% of herbal drink samples contained methyl alcohol (6). High concentrations of these herbal products may cause MP im people who consume these products for a long time (7).

EPIDEMIOLOGY

Alcoholics, persons with suicidal thoughts, toddlers and young children are individual at risk for MP. Alcoholics develop MP due to using illicitely produced alco-

hol with methanol instead of ethanol. MP is seen in suicidal attemps by ingestion of several industrial and household agents. Toddlers and young children are at risk of accidental ingestion of households containing methanol such as cologne, perfumes etc. (8). MP may be seen as individual cases as well as bulk outbreaks due to various reasons. Methanol intoxication outbreaks have been reported in underdeveloped countries as a result of adulteration of ethanol with methanol. Mass epidemics associated with MO are reported from around the world. One of the cases died due to shock, all of the patients received hemodialysis, but 18 of them died (9). During the beginning of COVID-19 pandemic, there has been a significant increase in the cases of morbidity and mortality from MP between February 2020 and April 2020 in Iran (10). In an 11 year retrospective review of 51 cases of MP, 74% were male.

PATHOPHYSIOLOGY

Methanol is absorbed in the gastrointestinal tract rapidly within 10 minutes after ingestion. Methanol does not bind to proteins and is directly absorbed into water component of the body with a rate of 0.7 L/Kg (Ashurst). The peak of serum concentrations occurs immediately after intaken. Methanol is metabolized in the liver through aldehyde and alcohol dehydrogenase but the metabolism process first begins with alcohol dehydrogenase in the gastric mucosa (11). Methanol is oxidized to formaldehyde by alcohol dehydrogenase, followed by oxidation of formaldehyde to formic acid by formaldehyde (12). Formaldehyde itself is toxic, but because it metabolizes to formic acid rapidly, it is not detected in body fluids after toxic ingestion. On the contrary, formic acid has a slow metabolism rate and therefore, it accumulates and exceed the capacity to be eliminated. There is a direct association between serum formic acid concentrations and MP. High serum concentrations of formic acid are associated with significant morbidity and mortality (13).

Formic acid formed is not easily eliminated and accumulates. A small amount of formic acid, known as formate, reacts with folate to produce water and carbon dioxide for exhalation. Unmetabolized part of methanol can not be sufficiently cleared by the kidneys or the lungs. Its effective half-life is between 30 and 85 hours (14).

Numerous factors determine the formic acid metabolism in humans. Dissociation of formic to format and a hydrogen ion occurs acid occurs at pH level. This is followed by metabolism of formate to carbon dioxide and water through folate. During this metabolic cycle, formate combines with tetrahydrofolate

($C_{19}H_{23}N_7O_6$) to dorm 10-formyl tetrahydrofolate. 10-formyl tetrahydrofolate dehydrogenase is then catalyzes the oxidation cycle and is enter the recycling of tetrahydrofolate again to complete the cycle (15).

Therefore, the oxidation of formate depends on hepatic concentrations of tetrahydrofolate. This is why MP induced in rats can not be extrapolated to humans. Human hepatic concentrations of tetrahydrofolate are nearly half of those in rats. Rats poisoned with methanol can metabolize format with a two-fold higher rate than humans. Hence, formic acid does not accumulate and as a consequence rats does not experience manifestations seen in humans following MP such as ocular effects, acidosis or other toxic effects (16). Folic acid supplementation improves the oxidation and it has been found to reduce the effects of MP (17).

TOXICOKINETICS

Absorption

The absorption of methanol following ingestion is rapid and occurs only within minutes of intake. The absorption process peaks within 30 to 60 minutes depending on the presence or absence of food intake with methyl alcohol. Methanol is well absorbed by the skin like all other organic solvents. Methanol is also well absorbed through inhalation with a mean absorption life of 0.80 hours (18). Pulmonary absorption occurs at 65-75% and does not reach 100%, due to absorvation of methanol by the upper respiratory tract mucosa.

DISTRIBUTION

Methanol has a distribution phase similar to that of water in the body as it is a water-soluble agent. The distribution volume of methanol is between 0.60 and 0.77 L/Kg. The mean distribution half-life of methanol is approximately 8 minutes after ingestion. The absorption and distribution of methanol in peak concentrations usually occurs at 30 to 60 minutes (19).

METABOLISM

Methanol itself is not toxic. The metabolism of methanol is responsible for the transformation to its metabolites. Methanol is mainly metabolized in the liver. Here, methanol isoxidized for formaldehyde through alcohol dehydrogenase. The oxidation of formaldehyde occurs via formaldehyde dehdyrogenase. The transformation of formaldehyde tp formic acid is very rapid and occurs within min-

utes. Formaldehyde itseld does not accumulate in the blood. Formate metabolism depends on the presence of tetrahydrofolate to form 10-formyl tetrahydrofolate, which can be metabolized to water and carbon dioxide. The half-life of formate in humans is as long as 20 hours (20).

CLINICAL PRESENTATION

History and Physical Exam

In early ingestions, receiving medical history is often challenging especially in people who ingested methyl alcohol intentionally or for self-harm purpose due to embarrassing (21). Many of these people may do not want to admit their intentions. On the other hand, accidental intakes are often witnessed and/or self-reported. (22). In the case of elevated anion gap, considering the diagnosis of MP depends upon the clinician's discrete.

In the latent period, which is between 12-24 hours of the ingestion, patients who present to the emergency department may appear normal. With the occurrence of acidosis, nausea/vomiting starts and is followed by abdominal pain and central nervous system depression. Ocular symptoms are often prominent and include blurred vision, decrased visual acuity and photophobia. Findings in physical examination include pupillaru defects, optic disc hyperemia and papilledema. If left untreated, patients progress to coma, circulatory and respiratory failure and death (23).

Clinical Manifestations

Clinical manifestation of MP begins within half to four hours after the ingestion. These symptoms include gastrointestinal disorders such as nausea/vomiting and abdominal pain and central nervous system suppression, which is prominent with confusion and drowsiness. Depending on the amount of ingestion, decompensated acidosis developes with diplopia, photophobia, blurred vision, and blindness (24). A patient with blurred vision but normal consciousness is suspected to have MP. A high anion gap metabolic acidosis may manifest later phases of the ingestion (19). Hyperkalemia and hyperglycemia may also be observed (25). In acute MP patients, neuroinflammation mediated by leukotriene (LT) may indicate in the mechanism of toxic brain injury (26). There is a significant correlation between serum LT concentration and prognosis of MP. Common clinical manifestations of MP are seen in Figure 2.

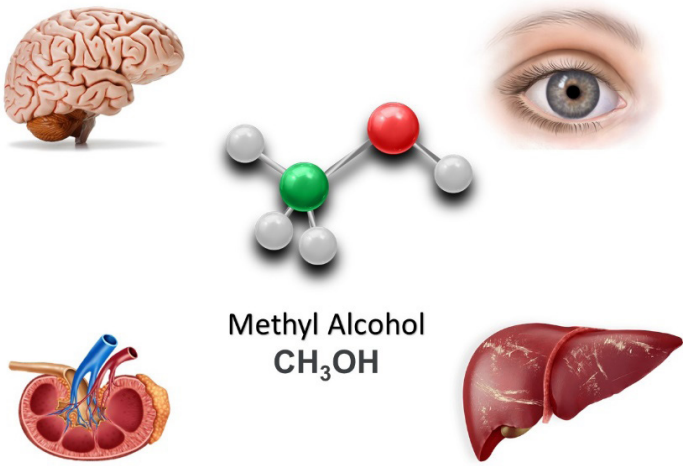

Figure 2. Clinical manifestation of methyl alcohol poisoning

Neurologic impairment

Alcohols with a higher molecular weight are more poisonous compared to those with a lower molecular weight. The absence of deep drunkenness does not rule out ingestion, particlularly in patients who drink alcohol chronically and therefore are tolerant to its effects on the central nervous system (27). A serum methanol concentration of 25-50 mg/dL indicate toxicity. The effects of MP on the central nervous systems are mediated by N-Methyl-D-aspartate receptors (NMDARs) and presynaptic GABA (GABA-A) receptors (27).

Metabolic acidosis

Metabolic acidosis with elevated osmol gap and anion gap is onne of the signs and symptoms of MP. Metabolic acidosis is resulted from the breakdown of methanol to formaldehyde and formic acid. Formic acid accumulation because of the absence of rapid pathway of alimination leads to acidosis (28).

Visual Impairment

Ocular toxicity is caused by untreated overdose methanol and is defined as pigmented retinal epithelial cells and destruction of optic nerve. Ocular toxicity leads to visual impairment ranging from blurred vision to complete blindness (29). Visual impairment caused by formate metabolites may manifest up to 72 hours after the ingestion. Visual impairment may be asymmetric. At physical examination, characteristic findings of visual impairment include papilledema, hyperemia, pallor of the optic disc and central scotoma. Optical coherence tomography

(OCT) may reveal swelling of the peripapillary nerve fibers and intraretinal fluid accumulation. One of the methanol metabolites, formate inhibits cytochrome oxidase, impairing oxidative phosphorylation. As the main cause of visual impairment in MP, retinal pigmented epithelial and optic nerve cells are uniquely susceptible. Disc pallor and optic nerve atrophy may be seen even years after the ingestion and even in those with normal intraocular pressure (30).

Brain Impairment

Following MP, CT scan or MRI examination of the patient reveals bilateral necrosis of the putamen and bilateral basal ganglia lesion. These injuries are not specific and may be seen due to hypoxia in other type of toxications; however, in MP these changes are observed without hypoxia and hypotension. Basal ganglia lesions observed in MP mat indicate Parkinson's disease developed by the patients later (31). Poor clinical outcome of patients with MP is associated with subcortex white matter necrosis and putamen bleeding. Cerebral impairment may be permanent in MP patients.

Kidney Impairment

Acute kidney injury and pancreatitis are reported in cases of MP. Acute kidney injury may be resulted from myoglobulinuria. This condition is associated with severe toxication and is evidenced by peak serum formate concentration, high initial osmolality and low initial serum pH (32).

Liver Impairment

Fatal MP cases may show pathological abnormalities of the liver, gastric mucosa and esophagus. Histopathological examination may reveal central hepatocyte necrosis, mild intrahepatic bile stasis, micro- and macrovesicular steatosis. Liver impairment due to MP is 6.3 times more common in men than in women (33).

DIAGNOSIS

Seum methanol levels may noy always rule out the diagnosis of MP, because serum concentrations are closely associate with the time of ingestion because of the rapid metabolism rate of methanol. Diagnosis of MP is based on history, clinical symptoms and laboratory findings. As mentioned above, history is not easy to receive always in some case especially in patient who intook methanol instead of ethanol or for suicidal purposes.

The presence of acidosis or acidemia may indicate MP. Serial serum bicarbonate change is also helpful. Ng et al. proposed that a person suspected for MP

should be examined every two to four hours for 12 hours (34). In addition, reduced bicarbonate levels without any other explanation may suggest an accumulation of formic acid as a results of the methanol metabolism. During MP, anion gap increases and osmolality gap decreases as formic acid accumulates (35). This dynamic process of methanol toxicity is an essential clinical feature

TREATMENT

Acticated charcoal or gastric lavage does not affcet MO poisoning because of rapid absorption. Treatment include the use of antidotes, folic acid to facilitate formic acid catabolism and hemoıdialysis to accelerate elimination of methanol (36). In addition, sodium bicarbonate is used for acidosis. Antidote therapy is initiated in the presence of acidosis or symptoms of organ dysfunction. In general, two types of antidote are used: ethanol and fomepizole. Ethanol is useful in reducing toxic metabolites of methanol (37). Fomepizole inhibits ADH enzyme which is among the modulators of methanol metabolism. In the case of severe methanol toxicity, hemodialysis is used as an integral part of the treatment. The goal of hemodialysis is to eliminate the primary combination and its toxic metabolites and to improve acidosis and thus, to reduce duration of treatment and hospitalization. Indications for hemodialysis include a primary methanol plasma concentration > 500 mg/L, kidney failure, visual impairment, and abnormal vital signs despite supportive care.

CONCLUSION

Despite advancements in treatment methods, methanol poisoning remains an important problem, causing significant morbidity and mortality especially in developing and underdeveloped countries where alcohol consumption is not legal or is expensive. Time between the ingestion and initiatig treatment is critical for the prognosis. Therefore, methanol intoxication should be taken into account in patients with neusea, vomiting, abdominal pain, mental fog, metabolic acidosis and increased anion gap, and the treatment should be started immediately. At the higher level, policies and strategies should be developed and implemented to raise people awareness of methanol poisoning and to discourage them for consuming such substances, and necessary regulations should be established.

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