

A Brief Review on Toxic Alcohols Management Strategies

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The information on burden of alcohol abuse in Iran is scarce. However, the available data show that mortality rates and frequency of its use have increased in the Iranian community. In particular, Iran occupies the 1st rank in the number of outbreak incidents and victims of toxic alcohols such as methanol in the Middle East. Mortality and morbidity of toxic alcohols are high if prompt diagnosis and treatment are not initiated rapidly. On-time diagnosis, proper case finding, and standard treatment have an essential role to reduce mortality and morbidity of toxic alcohols particularly blindness and other physical and psychological disabilities. This review focuses on intoxication with methanol, ethylene glycol, and isopropanol, and their treatment.

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INTRODUCTION

Alcohols are hydrocarbons that contain hydroxyl group. The term toxic alcohol (TA) traditionally refers to alcohols other than ethanol. The most common TA encountered clinically are methanol, ethylene glycol, and isopropanol.¹

The information on burden of alcohol abuse in Iran is scarce. However, the available data show that mortality rates and frequency of its use have increased in the Iranian community. In the first 6 months of 2010, 74 patients died due to complications of the acute alcohol overdose in Iran which shows a 23.3% increase in comparison with the same period in 2009.² It has also been claimed that the rate of positive respiratory alcohol test in 2010 was almost 28.6% more than that in the same period of time in 2009 (15 034 versus 11 696, respectively).³ The Iranian Police has announced that currently there are about 200 000 alcohol dependents in Iran and at least 60 to 80 million liters of different alcohol brands are smuggled into this country.⁴ These statistics do not include the hand-made and medicinal alcohols used country-wide. It seems that at least 1 000 000 users exist throughout Iran. Mean age for alcohol

use has decreased to 20 years and 26.5% of the youth who are currently alcohol users have had a positive history of alcohol abuse in their families.⁵ Different studies on youth populations in schools and universities showed that life-time abuse of alcohol varied between 7.4% and 42.5%.⁶⁻¹² This may eventually lead to exposure to TAs including methanol and ethylene glycol.^{13,14} A review on global TA outbreaks shows that Iran occupies the 1st rank in the number of methanol outbreak incidents and victims in the Middle East.¹³

Mortality and morbidity of toxic alcohols are high if prompt diagnosis and treatment are not initiated rapidly. Thus, all nephrologists and other health care professionals should be familiar with principles of diagnosis and treatment of toxic alcohol poisoning. On-time diagnosis, proper case finding, and standard treatment have an essential role to reduce mortality and morbidity of toxic alcohols particularly blindness and other physical and psychological disabilities.^{1,15-22}

SOURCE OF TOXIC ALCOHOLS

Methanol is used as a solvent in printing and copy solutions, adhesives, paints, polishers, disinfectants,

and stabilizers. It is also used in window cleaners, antifreeze, as a fuel in alcoholic lamps, and as an additive in gasoline. Methanol is known as an industrial alcohol and is mixed up with ethanol that is used for medical purposes.^{1,16,23} There were large epidemics of methanol due to contamination of antidiarrheal medication in India.²¹ The so called 'standard alcoholic drinks' sold in black markets in many countries may contain methanol. The traditional herbal extracts may contain methanol due to cellulose fermentation of the stalks and seeds of the herbs. The estimated minimum lethal dose for adults is approximately 10 mL, but there are reports of patients surviving ingestions greater than 400 mL without sequelae.^{15,23}

Ethylene glycol is a sweet-tasting alcohol that is a common constituent of antifreeze or deicing solutions. It is also used in the chemical synthesis of plastics, films, and solvents. It can be found in many products including solvents, paints, and coolants. The estimated minimum lethal dose for adults is approximately 100 mL but many patients survived even with larger amounts up to 3 L.^{9,19,24}

Isopropanol is a colorless liquid with a bitter taste primarily available as rubbing alcohol, typically as a 70% solution. It is used in the production of acetone and glycerin. The estimated minimum lethal dose for adults is approximately 100 mL,

but patients have survived ingestions of over 1000 mL. Case fatality ratio of isopropanol is less than methanol and ethylene glycol.^{20,24}

ABSORPTION, DISTRIBUTION, AND METABOLISM

All toxic alcohols are rapidly absorbed through gastrointestinal tract. Dermal absorption is more feasible for isopropanol, methanol, and glycol ethers. Except isopropanol, they are not toxic by themselves, but their metabolites are toxic (Figure 1). Without intervention, toxic alcohols are primarily eliminated through successive metabolism by alcohol dehydrogenase (ADH) mainly in the liver. It can change the parent compound (ie, methanol and ethylene glycol) to a toxic metabolite, or in case of isopropanol, to a less toxic metabolite. Methanol and ethylene glycol may also be eliminated from the body as unchanged parent compounds. Any substance that blocks ADH or deviates it to metabolize more favorable substance (ethanol) will prolong half-lives. All toxic alcohols are water-soluble and have a volume of distribution of 0.6 L/kg, equal to that of total body water. Therefore, extracorporeal techniques will be able to remove them from serum.^{1,15-23}

The average absorption half-life of methanol is 5 minutes and reaches maximum serum concentration

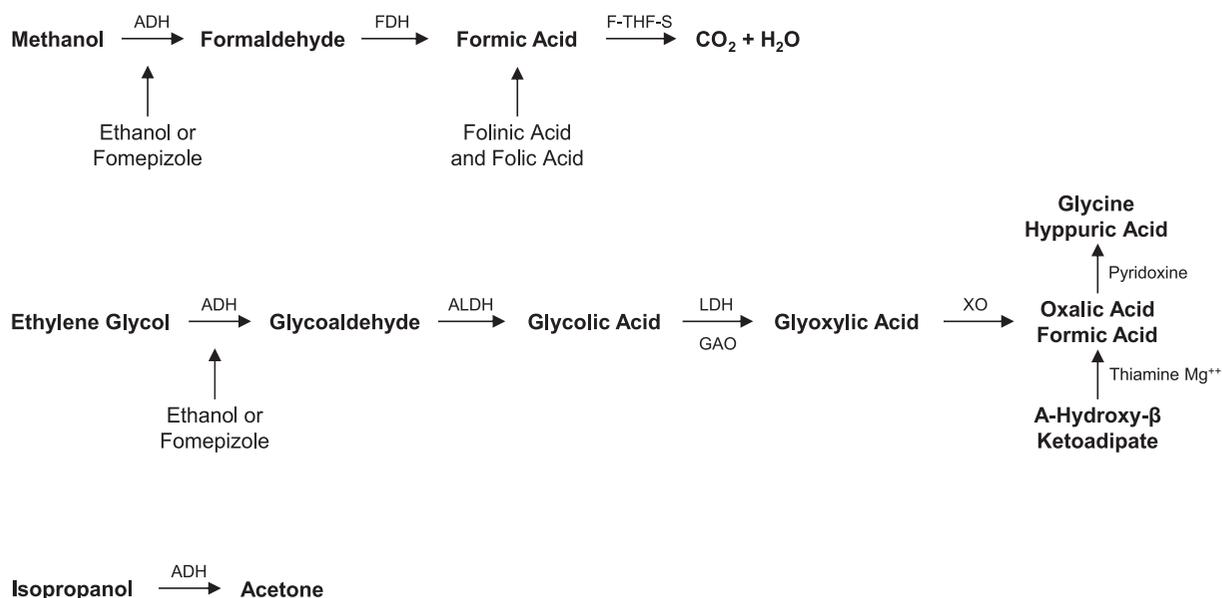


Figure 1. Metabolism of toxic alcohols and mechanism of action of antidotes. ADH indicates alcohol dehydrogenase; FDH, formaldehyde dehydrogenase; F-THF-S, 10-formyl tetrahydrofolate synthetase; ALDH, aldehyde dehydrogenase; LDH, lactate dehydrogenase; GAO, glycolic acid oxidase; and XO, xanthine oxidase.

within 20 to 60 minutes and well dissolves in body water. It may be absorbed by inhalation. Methanol does not have significant renal elimination and is cleared much more slowly than ethylene glycol as a vapor in expired air (half-life of 30 to 54 hours).^{1,16,23}

Ethylene glycol reaches a peak serum level in 4 ± 2 hours after ingestion. It is oxidized by alcohol dehydrogenase in the presence of nicotinamide adenine dinucleotide to glycoaldehyde, which is then rapidly oxidized to glycolate. When kidney function is normal, ethylene glycol is slowly cleared by the kidneys with a half-life of approximately 11 to 18 hours.^{1,17,19,24}

Isopropanol reaches a peak serum level in 30 ± 15 minutes after ingestion. Isopropanol is oxidized by ADH to acetone. The elimination half-life of isopropanol is 7 ± 3 hours, but is prolonged with ethanol co-ingestion. Elimination of acetone is much slower due to excretion in the breath and urine.^{1,20,24}

CLINICAL MANIFESTATIONS

All alcohols may cause inebriation depending on the dose. Higher molecular-weight alcohols are more intoxicating (eg, isopropanol \approx ethylene glycol $>$ ethanol $>$ methanol). Absence of apparent inebriation does not exclude toxic alcohol ingestion. Severe metabolic acidosis with high anion gap and increased osmolality strongly suggest methanol and or ethylene glycol poisoning. Both ethylene glycol and methanol are neurotoxic and neuro-imaging studies may reveal basal ganglia involvement after a while.^{1,16,24,25}

Clinical manifestations of poisoning with methanol alone initiate within 0.5 to 4 hours of ingestion and include nausea, vomiting, abdominal pain, confusion, drowsiness, and central nervous system suppression. Patients may not seek help at this stage. Clinical manifestations may be delayed for days, particularly if ethanol has also been ingested. Absence of symptoms in the hours following a potentially toxic dose does not preclude toxicity. After a latent period of 6 to 24 hours that depends on the dose absorbed, decompensated metabolic acidosis occurs with blurred vision, photophobia, changes in visual field, accommodation disorder, diplopia, early or late blindness, and less commonly, nistagmus. Blurred vision with normal consciousness is a strong suspicious sign of methanol poisoning. Co-ingestion of ethanol delays methanol poisoning

features for more than 24 hours and sometimes up to 72 hours. Severity of clinical manifestations and mortality associated well with severity of central nervous system depression, hyperglycemia, and metabolic acidosis, but not with serum methanol concentration.^{1,16,23,26,27}

The clinical course of ethylene glycol intoxication is divided into 3 stages. First, inebriation like ethanol (1 to 2 hours); second, glycoaldehyde and glycolate production and initiation of cardiopulmonary, metabolic (acidosis), and central nervous system (coma, seizure) toxic effects (12 to 24 hours); and third, oxalate production and the most prominent end-organ effect of ethylene glycol that is nephrotoxicity characterized by flank pain, acute tubular necrosis, hypocalcemia, and kidney failure. The oxalic acid metabolite forms a complex with calcium to precipitate as crystals in the renal tubules leading to acute kidney failure (24 to 72 hours). Direct tubular toxicity may also occur. Other effects include hypocalcemia and QTc prolongation with dysrhythmias and cranial nerve abnormalities.^{1,17,19,24}

Many patients intoxicated with isopropanol will have “fruity” breath from the metabolite elimination via breathing. Unlike other toxic alcohols, most of the clinical manifestations in isopropanol intoxication are due to the parent compound not its metabolite acetone. The clinical signs of isopropanol intoxication will occur within 1 hour of ingestion and include effects on the central nervous system (ataxia and loss of consciousness), gastrointestinal system (nausea, vomiting, and gastritis, even hemorrhagic one), and cardiovascular system (hypotension due to cardiac depression). Hypotension is the strongest predictor of mortality. High osmol gap, ketonemia or ketonuria with no metabolic acidosis, fruity or sweet odor on the breath, and loss of consciousness may bring the diagnosis up.^{1,20,24}

Differential Diagnosis

An important point in management of methanol poisoning is proper and early diagnosis. Since emergency estimation of serum methanol concentration may not be available, clinical differential diagnosis is very important.¹⁷

Time of admission and patient’s condition. All alcohols are rapidly absorbed and clinical features after overdose such as flushing, drunk

behavior, central nervous system depression, and gastrointestinal dysfunction may occur within 1 to 2 hours. In ethanol poisoning, the patient's condition is gradually improved, whereas in toxic alcohols, it will be deteriorated over time even after 24 hours (ie, methanol).

Drunken behavior and vasodilatation. In ethanol poisoning, the patient has flushing and is talkative and aggressive, whereas in most toxic alcohol cases, no sign of drunk behavior is observed in late phases and a state of shock with chills and cold extremities is noted.

Ophthalmic manifestations. In ethanol intoxication, pupils are usually miotic and there is no visual defect, whereas in methanol poisoning, pupils are mydriatic and there is a retarded reaction or no response to light.

Smell of alcohol. Smell of alcohol is less noted in toxic alcohols except for isopropanol (fruity breath). Distilled ethanol has a specific odor which is usually not mistaken with toxic alcohols.

Convulsions and central nervous system symptoms. Central nervous system symptoms, particularly convulsions, are the signs of severity of methanol and other toxic alcohol intoxications.

Tachypnea and acidemia. Acidemia is a good laboratory finding in differential diagnosis of toxic and nontoxic alcohols. Body response to acidemia is tachypnea and hyperventilation. However, in ethanol poisoning, mild acidemia may occur but is usually self-limited and improves with supportive treatments.

Serum alcohol levels. Estimation of serum alcohol level is probably important in early hours of intoxication but is practically less important as the time passes and may even be confusing. Since the toxic metabolites are responsible for the complications (except for isopropanol), parent toxic alcohol concentrations may be decreased at the time of admission and the toxic metabolites may be increased. In addition, improper sampling such as using alcohol as a skin disinfectant may cause false increase in alcohol levels.²⁸

Blood glucose, electrolytes, and osmolar and anion gaps. An osmolar gap more than 10 mOsm/kg is suggestive of ethylene glycol, methanol, isopropanol, ethylene oxide, or acetone toxicity.¹⁸ A high anion gap metabolic acidosis may be revealed at later stages of methanol and ethylene glycol poisoning. Hypoglycemia may be detected with

ethanol and isopropanol, while hyperglycemia and hypocalcemia may be detected in methanol and ethylene glycol poisonings, respectively. Hyperkalemia due to acidosis is observed in methanol and ethylene glycol poisoning, whereas hypokalemia due to vomiting may occur in ethanol intoxication.²⁸ Urine calcium oxalate crystals can be seen in ethylene glycol intoxication. These findings should be evaluated together with the other manifestations and observations.

TREATMENT

General Considerations

Initial evaluation should be focused on the improvement of vital signs: airway, respiration, and circulation. Basic antidotes that may be useful in different phases have been shown in Figure 1. It should be noted that blocking ADH in toxic alcohol pathway would be useful if the metabolites are more toxic than the parent toxic alcohols (such as cases with methanol and ethylene glycol). Isopropanol is more toxic than acetone, and therefore, ADH blockers would be unnecessary and even harmful. On the other hand, antidotes in the early phases may not be useful if the patients come in late stages. For example, ethanol will not be useful if all methanol/ethylene glycol is already converted to formaldehyde or glycolaldehyde. Fortunately, hemodialysis removes all parent toxic alcohols and their metabolites although at the first few hours postdialysis, redistribution of methanol may result in elevation of methanol concentrations.²⁹ Hemodialysis does not improve sequelae if all toxic alcohols and their toxic metabolites are already wiped out. This concept is essential to decide on which therapy would be useful and who will benefit from hemodialysis, particularly in mass poisonings. In case of hemodialysis, ethanol doses should be increased up to 2 folds if it has been started for methanol or ethylene glycol blockade.^{1,15-24}

Methanol

The Table shows indications for ethanol and fomepizole. In general, ethanol and fomepizole have the same efficacy in treatment of the toxic-alcohol-poisoned patients, but fomepizole is preferred in those with loss of consciousness as it does not induce decreased consciousness, per se. In Figure 2, algorithm of standard treatments of methanol poisoning is illustrated. In case of

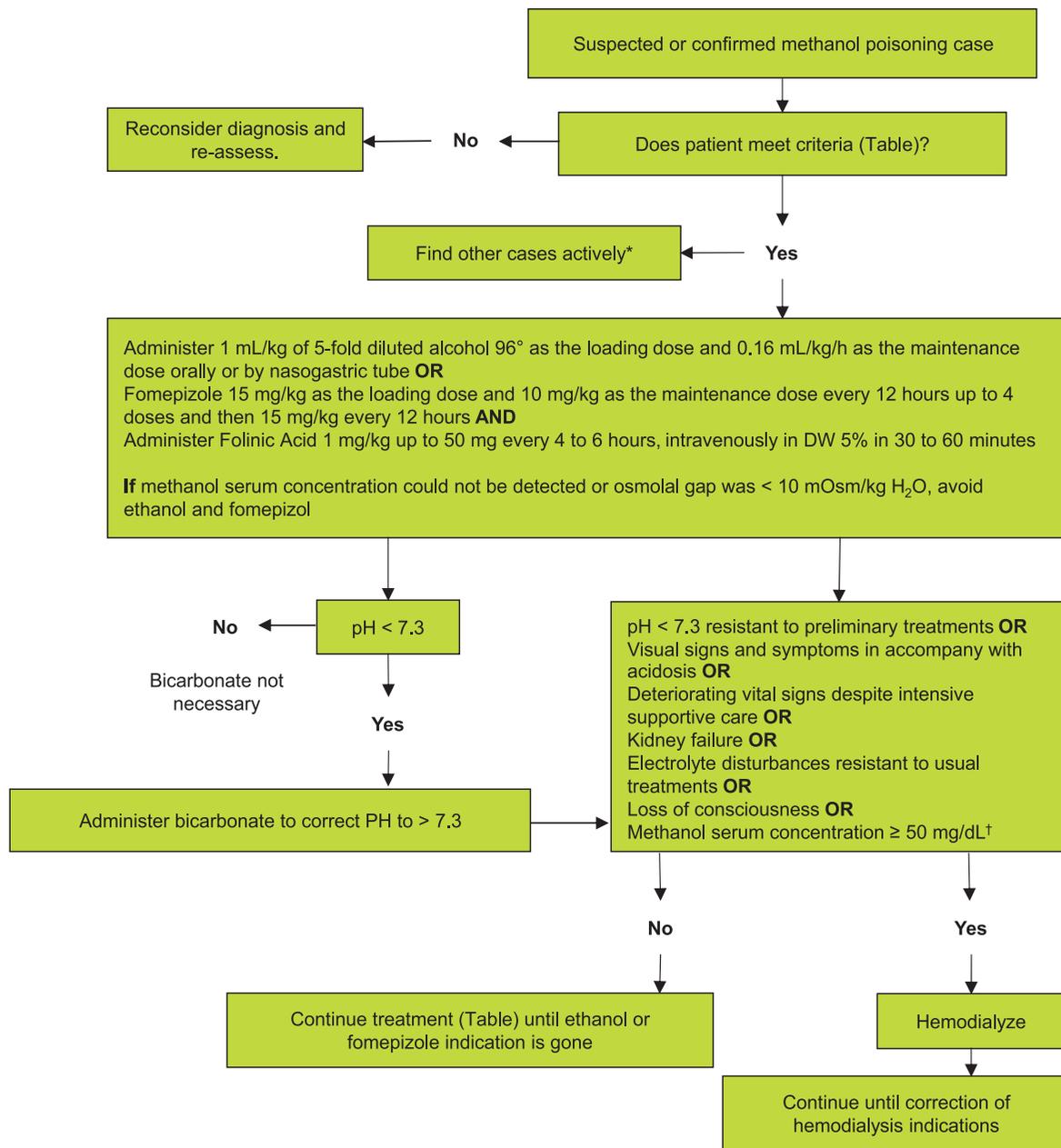


Figure 2. Algorithm of methanol poisoning treatment.

*The aim of case finding is to access at-risk patients who have not been referred to the hospital. This could be performed via confidential consultation with the patient or the relatives. The patients and their relatives should be educated about the risk of methanol poisoning and be asked to help in finding new possible patients who might have ingested toxic alcohol. Every suspected or confirmed methanol poisoning case should be reported to the University patients' referral committee.

†Although serum methanol concentration higher than 25 mg/dL ethanol-treated patients is an indication for hemodialysis, hemodialysis can be deferred for fomepizole-treated patients. However, it may prolong their hospitalization period.

metabolic acidosis, sodium bicarbonate should be administered.^{1,23}

Ethylene Glycol

Ethanol, fomepizole, and bicarbonate are initiated with the same indications and doses as in methanol poisoning (Table). Urine calcium oxalate crystals

have the same value as osmolar gap and can be used interchangeably to start ADH blockers. Due to increased risk of calcium oxalate formation, asymptomatic hypocalcemia does not need any intervention. Although seizure may be revealed as a result of hypocalcemia, the first-line treatment would be benzodiazepines. Pyridoxine (100 mg/d,

Indications of Ethanol and fomepizole for Methanol Poisoning

Criteria
Serum methanol concentration of > 20 mg/dL OR
History of toxic dose ingestion and osmolal gap >10 mOsm/kg H ₂ O OR
History or high suspicion* of methanol poisoning if the patient is admitted within 72 hours of ingestion and has had two of the following criteria:
<ul style="list-style-type: none"> ● Arterial pH < 7.3 ● Serum bicarbonate < 20 mEq/L ● Osmol gap > 10 mOsm/kg H₂O

*The authors recommend that in case of methanol poisoning epidemics, any clinically suspicious case should be treated.

intravenous) and thiamine (100 mg/d, intravenous) may be beneficial, specifically in malnourished patients. Patients with metabolic acidosis (pH < 7.3) or deteriorating clinical status with respiratory failure or hypotension, as well as those with acute kidney failure unresponsive to standard therapy should be considered for hemodialysis. Continuous or prolonged hemodialysis may be required for severe acidosis or high level of ethylene glycol and its toxic metabolites. Those patients with normal kidney function and no metabolic changes may be treated with fomepizole even if the ethylene glycol level is more than 20 mg/dL but need close monitoring.^{1,17,19,24}

Isopropanol

Other than supportive therapy, hemodialysis is indicated for patients with an isopropanol level greater than 400 mg/dL and profound central nervous system depression, kidney failure, or resistant hypotension.^{1,20,24}

CONCLUSIONS

In case of any toxic alcohol intoxication, active finding of other patients or victims and identification of the origin is very important, which require intersectoral cooperations. Case finding protocols will rescue patients and reduce toxic alcohol sequelae in early stages when inexpensive antidotes like ethanol are available. The golden time for treating toxic alcohols is limited and by running the time, the probability of death, blindness, kidney failure, and central nervous system damage will increase. Correct diagnosis, attention to the probable source of toxic alcohol, and proper cases finding to treat outpatient cases will decrease mortality and morbidity.

CONFLICT OF INTEREST

None declared.

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