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METHANOL GUIDELINES—AACT/EAPCCT

American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Methanol Poisoning

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ABSTRACT

***Epidemiology**: Almost all cases of acute methanol toxicity result from ingestion, though rarely cases of poisoning have followed inhalation or dermal absorption. The absorption of methanol following oral administration is rapid and peak methanol concentrations occur within 30–60 minutes. **Mechanisms of Toxicity**: Methanol has a relatively low toxicity and metabolism is responsible for the transformation of methanol to its toxic metabolites. Methanol is oxidized by alcohol dehydrogenase to formaldehyde. The oxidation of formaldehyde to formic acid is facilitated by formaldehyde dehydrogenase. Formic acid is converted by 10-formyl tetrahydrofolate synthetase to carbon dioxide and water. In cases of methanol poisoning, formic acid accumulates and there is a direct correlation between the formic acid concentration and increased morbidity and mortality. The acidosis observed in methanol poisoning appears to be caused directly or indirectly by formic acid production. Formic acid has also been shown to inhibit cytochrome oxidase and is the prime cause of ocular toxicity, though acidosis can increase toxicity further by enabling greater diffusion of formic acid into cells. **Features**: Methanol poisoning typically induces nausea, vomiting, abdominal pain, and mild central nervous system depression. There is then a latent period lasting approximately 12–24 hours, depending, in part, on the methanol dose ingested,*

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following which an uncompensated metabolic acidosis develops and visual function becomes impaired, ranging from blurred vision and altered visual fields to complete blindness. ***Management****: For the patient presenting with ophthalmologic abnormalities or significant acidosis, the acidosis should be corrected with intravenous sodium bicarbonate, the further generation of toxic metabolite should be blocked by the administration of fomepizole or ethanol and formic acid metabolism should be enhanced by the administration of intravenous folinic acid. Hemodialysis may also be required to correct severe metabolic abnormalities and to enhance methanol and formate elimination. For the methanol poisoned patient without evidence of clinical toxicity, the first priority is to inhibit methanol metabolism with intravenous ethanol or fomepizole. Although there are no clinical outcome data confirming the superiority of either of these antidotes over the other, there are significant disadvantages associated with ethanol. These include complex dosing, difficulties with maintaining therapeutic concentrations, the need for more comprehensive clinical and laboratory monitoring, and more adverse effects. Thus fomepizole is very attractive, however, it has a relatively high acquisition cost.* ***Conclusion****: The management of methanol poisoning includes standard supportive care, the correction of metabolic acidosis, the administration of folinic acid, the provision of an antidote to inhibit the metabolism of methanol to formate, and selective hemodialysis to correct severe metabolic abnormalities and to enhance methanol and formate elimination. Although both ethanol and fomepizole are effective, fomepizole is the preferred antidote for methanol poisoning.*

EPIDEMIOLOGY

Almost all cases of acute methanol toxicity result from ingestion. It may result from methanol contamination of grain spirits, consumption of methanol-containing fluids by alcoholics deprived of their alcoholic beverage of choice, suicidal ingestion of methanol containing products and unintended consumption of such products by children. Methanol is cheaper than ethanol and may be used to fortify illicit spirits. Prisoners and others may substitute methanol-containing products for alcoholic beverages when ethanol is in short supply. Mass epidemics associated with these circumstances are reported from around the world.[1–8] Rare cases of inhalational[9–12] or dermal[13–15] toxicity are reported.

Small amounts of methanol may be taken in with food. Dietary sources include fresh fruit and juices, vegetables, and dietary products containing aspartame.[16] Methanol is also a natural fermentation product and small amounts are found in all spirits.[16] Even in these small amounts it is thought to be a cause of a hangover.[16–18] After binge drinking, serum methanol concentrations build up, but do not reach concentrations usually associated with acidosis and ophthalmolgical dysfunction.[19–21]

The American Association of Poison Control Center's Toxic Exposure Surveillance System includes 2418 reports of methanol exposure from 2000.[22] Of these, 209 were intentional. One hundred ninety-three patients suffered moderate or major toxicity and 12 died. With the exception of a 3-month-old child who died as a result of unintended reconstitution of his formula with methanol instead of water, all deaths occurred in those over 25 years of age. The intention of four of these victims was unknown, three intended abuse, and the other four suicide. This database is derived from a population base of 271 million, but because reporting is voluntary it is likely that many significant exposures, including deaths, are not reported.

In comparison, deaths from methanol in the province of Ontario with a population of 11 million, averaged seven per year over the period 1986–1991. Of 43 methanol related deaths identified in a six year review of the Ontario Provincial Coroner's Office records, 22 were associated with suicidal ingestion and 14 consumed labeled, methanol containing products as substitutes for ethanol.[23] Three victims ingested methanol improperly stored in containers normally used for ethanol and five others had consumed contaminated illicit liquor. All were over 18 years of age and 91% were men.[23]

In an 11-year, retrospective review of all admissions to an adult hospital for methanol ingestion, 74% of the 51 patients identified were male. One presented with shock and died, all of the others received hemodialysis but 18 died.[24] Outcome was related to the degree of illness as manifested by acidosis, coma, and seizures at the time of presentation.[24] Epidemiological data derived from retrospective reviews of hospital-based series may be biased by age distribution seen at the facility. Outcome in other reports may be biased by the time to presentation if prompted by a mass exposure.

Physical Properties

Methanol (methyl alcohol, H_3COH, CAS #67-56-1) is a clear, colorless liquid at room temperature. It has a faint, slightly alcoholic odor.[16] Methanol is known as wood alcohol because it was distilled from wood in the 1920s and 1930s. Today, almost all methanol is made synthetically by the catalytic reduction of carbon monoxide or carbon dioxide in the presence of hydrogen.[16] Methanol has a molecular weight of 32 g/mol.[16] It is less dense than water (0.79 g/cc at 4°C) and boils at 65°C. It is freely miscible with water, ethanol, and many organic solvents.[16]

Sources and Uses

In the United States, over a billion gallons of methanol are produced annually. The majority of it is used as a solvent, an intermediate in the manufacture of other chemicals, or as an octane booster in reformulated gasoline. It has an octane rating from 106 to 115 and has been advocated as a less polluting fuel.[25] As a solvent it is present in cleaning solutions, printing and duplicating solutions, adhesives, enamels, stains, dyes, varnishes, thinners, and paint removers.[16] Many of these products are found in the home. It is also widely available as an antifreeze agent in windshield wiping fluids, a gas line antifreeze, a gasoline additive, and as a fuel for camp stoves and chafing dishes.[16]

Toxicokinetics

The pharmacokinetics of methanol have been well defined in humans.[26–40] Therefore, contemporary literature[26,41–46] that addresses the pharmacokinetics and toxicokinetics of methanol in nonprimate animal models has minimal application value in the management of methanol poisoning in humans. Furthermore, there are profound species differences[47–49] in the metabolism of methanol that makes interpretation of data and extrapolation to humans invalid. For example, in rats a catalase–peroxidase system is operative in the initial metabolic step. In contrast, alcohol dehydrogenase catalyzes the initial metabolic conversion in primates.[50] Therefore, pharmacokinetic research that relies on nonprimates is not applicable and not addressed.

Absorption

The absorption of methanol following oral administration is rapid with a mean absorption half-life of 5 minutes.[27] Depending on the presence or absence of food, peak absorption occurs within 30–60 minutes.[47,51] Like other organic solvents it is relatively well absorbed through the skin.[28] Methanol is well absorbed by the inhalation route[29,30] with a mean absorption half-life of 0.80 hours when volunteers inhaled methanol 200 ppm for 4 hours.[30] It is estimated that the pulmonary absorption fraction is 65–75%.[42] Absorption is not 100% because methanol is water-soluble and some of it is absorbed by the mucous in the upper respiratory tract.[31]

Distribution

Methanol is water-soluble and has a distribution phase analogous to the body water. The volume of distribution is approximately 0.60–0.77 L/kg.[27,50,52] Following ingestion, methanol has a mean distribution half-life of 8 minutes.[27] The rapid absorption and distribution of methanol results in peak concentrations within 30–60 minutes.

Metabolism

Methanol has relatively low toxicity. Metabolism is responsible for the transformation of methanol to its toxic metabolites. Methanol is metabolized in a sequential fashion, principally in the liver.[32] Alcohol dehydrogenase is the primary enzyme responsible for the oxidation of methanol to formaldehyde.[53] The oxidation of formaldehyde to formic acid is facilitated by formaldehyde dehydrogenase.[53] The conversion of formaldehyde to formic acid is very rapid with a half-life of 1–2 minutes.[54–56] There does not appear to be any accumulation of formaldehyde in the blood. Formate metabolism is dependent upon the presence of tetrahydrofolate to form 10-formyl tetrahydrofolate that can be metabolized to carbon dioxide and water or alternative metabolic pathways.[57,58] The half-life of formate has been as long as 20 hours in humans[59] (Fig 1).

Elimination

The pharmacokinetics of methanol elimination in the poisoned patient are best characterized by zero-order kinetics.[60,61] However, at low concentrations first-order kinetics prevail.[34,35] A 5-week-old infant with an extraordinarily high methanol concentration had an average rate of elimination that was best characterized by first-order kinetics. The authors speculated that the observed first-order kinetics could not be explained through the metabolic action of alcohol dehydrogenase and postulated that the infant must have had an alternate nonsaturated mechanism of elimination.[35] In the poisoned patient, the apparent elimination half-life approximates 24 hours.[25,62,63] At low concentrations, first-order kinetics prevail with an elimination half-life of 1–3 hours.[26,32,36,57] Following the inhalation of methanol, 200 ppm (NIOSH permissible exposure limit), by volunteers, the mean elimination half-life was 3.7 hours,[30] consistent with the half-life associated with the ingestion of small quantities of methanol. In a study where subjects inhaled methanol, 800 ppm for 0.5–2.0 hours, the mean elimination half-lives from blood (1.44 hours), urine (1.55 hours), and breath (1.40 hours) were similar and followed first-order kinetics.[32] At low concentrations, there is no apparent clinical difference in methanol metabolism between ethanol abusers and nonethanol abusers.[36–38,57] A case report by Jacobsen and colleagues determined that the total body clearance of methanol was 11.3 mL/min.[40] The half-life of formate has been as long as 20 hours in humans. In a methanol poisoned patient, formate elimination followed first-order kinetics during hemodialysis and resulted in a plasma half-life of 165 minutes.[64] It has been proposed that the slow clearance of formic acid may be a consequence of zero-order kinetics that are operative in the metabolism of both methanol and formic acid, possibly in combination with the continuous recycling of formic acid and protons with chloride ions in the kidney.[50] The persistence of formic acid provides a biomarker to monitor and assess occupational and poisoning exposures to methanol.[39,65] However, when the methanol air concentration is low, the presence of methanol in the urine is a more sensitive indicator of exposure than urinary formic acid.[66]

MECHANISMS OF TOXICITY

The Role of Formic Acid

Methanol is metabolized to formaldehyde and then to formic acid. Although formaldehyde itself is potentially toxic, due to its rapid metabolism to formic acid, it has not been detected in body fluids after toxic methanol ingestions.[54] Formic acid is metabolized more slowly and, therefore, accumulates as the generation of formic acid exceeds the capacity to eliminate it. Tephly[67] found a direct correlation between formic acid accumulation and the toxicity of methanol. This was confirmed by Brent and colleagues[53] who also identified a direct relationship between increased morbidity and mortality and the presence of high serum formic acid concentrations.

There are a number of factors that control the rate of formic acid metabolism in humans. At physiological pH, formic acid dissociates to formate and a hydrogen ion. Formate is subsequently metabolized to carbon dioxide and water by a folate-dependent mechanism. Formate enters this metabolic cycle by combining with tetrahydrofolate to form 10-formyl tetrahydrofolate.[68] Hence, the oxidation of formate is dependent on hepatic tetrahydrofolate concentrations, which are controlled by two main factors. Firstly, the presence of adequate dietary folic acid (tetrahydrofolate is derived from folic acid),[69] and secondly, the

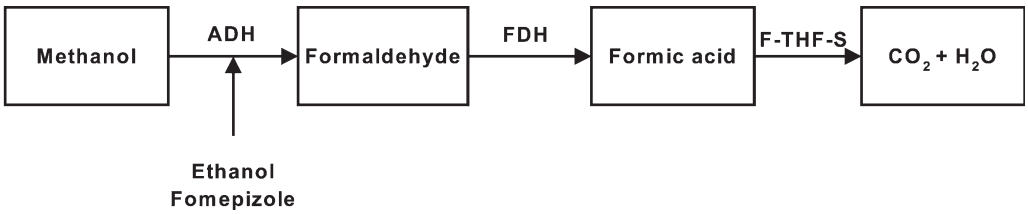

Figure 1. Metabolism of methanol.

efficiency with which tetrahydrofolate is regenerated during formate oxidation.

10-Formyl tetrahydrofolate dehydrogenase catalyzes the final step in the oxidation of formate and is involved in the recycling of tetrahydrofolate.[70] Human hepatic tetrahydrofolate concentrations are approximately half those in the rat and, in addition, humans also have lower 10-formyl tetrahydrofolate dehydrogenase activities than rats. As rats poisoned with methanol can metabolize formate at twice the rate of humans,[71] formic acid does not accumulate and as a consequence rats are not susceptible to the ocular effects, acidosis, or other toxic manifestations observed in humans.[72] On the contrary, folate-deficient rats are more susceptible than normal rats to the toxic effects of methanol as formic acid accumulates and acidosis supervenes.[73] Conversely, supplementation with folic acid enhances the oxidation of formate in a variety of species including the monkey[48] and in humans[14], and has been found to reduce the toxicity of methanol.[74] These studies confirm the importance of formic acid in the toxicity of methanol in man and the potential usefulness of folate in the treatment of methanol poisoning.[14,75]

Formic Acid Inhibition of Cytochrome Oxidase

Nicholls[76] has demonstrated that formic acid can inhibit cytochrome c oxidase activity in intact mitochondria, in submitochondrial particles, and in isolated cytochrome aa_3. Formic acid binds to the sixth coordination position of ferric heme ion in cytochrome oxidase, thus, preventing oxidative metabolism.[77] Röe[78] postulated that this was due to the affinity of formic acid for ferric iron moiety. This affinity is also thought to cause the methemoglobinemia seen rarely in cases of severe methanol poisoning.

The inhibition of cytochrome oxidase complex at the terminal end of the respiratory chain in the mitochondria leads to "histotoxic hypoxia." The binding of formic acid to cytochrome oxidase is similar to that seen with other toxins such as cyanide, hydrogen sulfide, and carbon monoxide, although formic acid is a less potent inhibitor.[79] The inhibition of cytochrome oxidase by formic acid increases with decreasing pH. This suggests that the active inhibitor is the undissociated acid as the concentration of the latter increases with fall in pH and as the inner membrane of the mitochondria is only permeable to the undissociated acid.[76] Therefore, as the pH falls, cytochrome oxidase inhibition is potentiated and the onset of cellular injury is hastened.[50]

Etiology of Acidosis

There has been much debate as to whether formic acid contributes directly to the metabolic acidosis observed in methanol poisoning, or if the acidosis is due mainly to the secondary effects of formate causing a lactic acidosis.[55] The magnitude of the acidosis correlates well with formic acid accumulation[80] and the decrease in plasma bicarbonate closely parallels the increase in the plasma formic acid concentration,[47,81,82] suggesting that the acidosis seen early in the clinical course is caused directly by formic acid production.[55,83]

The accumulation of formic acid can cause an acidosis directly by delivering protons as it dissociates to formate and hydrogen ions. As homeostatic mechanisms compensate for the increasing acidemia, the homeostatic reserve becomes exhausted so that the acidosis can no longer be compensated.[25]

Lactate is produced as formic acid interferes with intracellular respiration and promotes anaerobic metabolism. As lactate concentrations rise and tissue hypoxia increases, the pH falls further and leads to the generation of more undissociated formic acid.[84] A falling pH enhanced by lactate production will also increase formic acid diffusion across cell membranes leading to further central nervous system (CNS) depression with hypotension and increased lactate production. It has also been suggested that the severity of lactic acidosis may be increased due to the increased redox state of the body tissues with an increased ratio of NADH to NAD + secondary to the oxidation of methanol and formaldehyde. The increase in the redox state would force conversion of pyruvate to lactate by stimulating anaerobic glycolysis.[85]

Both formate and lactic acid contribute to the anion gap increase seen in methanol poisoning. The early acidosis observed in methanol poisoning may be due to the accumulation of formate, with lactate accumulation occurring in the later stages of poisoning from tissue hypoxia and inhibition of cellular respiration by formic acid.[82]

Formic Acid-Induced Ocular Toxicity

Although it was suggested initially that formaldehyde was the causative agent in methanol ocular toxicity,[86] in vivo studies have implicated formic acid.[55,75,82,87–89] Ocular toxicity appears to be caused by formic acid directly and not by the metabolic acidosis that accompanies its accumulation.[90] However, acidosis can increase toxicity further by enabling greater diffusion

of formic acid into cells. Vision can improve if acidosis is corrected as this produces larger amounts of dissociated formic acid that does not diffuse as easily as the undissociated formic acid.[75]

Undissociated formic acid specifically targets the optic disc and retrolaminar section of the optic nerve, causing optic disc edema, breakdown of the myelin sheaths and optic nerve lesions.[91,92] Retinal dysfunction, documented by visual evoked potentials (VEP) and electroretinograms (ERG), occurs at lower formic acid concentrations than optic neuropathy.[93–95]

The undissociated formic acid binds to cytochrome oxidase causing histotoxic hypoxia, thereby inhibiting retinal and optic nerve mitochondrial function and depleting retinal and optic nerve ATP.[96] The depletion of ATP reduces the activity of the membrane Na–K ATPase pump, which halts conduction of the action potential, damages the myelin sheaths and causes loss of vision.[97] It also leads to stasis of axoplasmic flow that results in intra-axonal swelling and optic disc edema.[92,97] As myelin sheaths are damaged, they start to swell causing a compression-type injury to the nerve fibers. This prevents further axoplasmic flow of proteins, mitochondria and neurotubules from the cell body to the fiber of the axoplasm. As cells become deficient in these essentials they become more susceptible to formic acid-induced injury,[92,98,99] which causes neuronal conduction deficits and loss of vision.[89]

The selective damage to the retrolaminar optic nerve and retina may be caused by an increased exposure to formic acid due to a copious blood flow through the choriocapillaris and from the cerebral spinal fluid,[97] thereby allowing formic acid to diffuse to the adjacent optic disc and the retrolaminar section of the optic nerve. These cells are also selectively vulnerable to histotoxic hypoxia as optic nerve fibers and their myelin sheaths have fewer mitochondria and low reserves of cytochrome oxidase due to their low metabolic requirements.[25,89]

Neurotoxicity

Magnetic resonance imaging (MRI) and computed tomography (CT) scans and pathological findings at autopsy[81,100–102] have revealed signs of edema and necrotic damage to the basal ganglia of the brain, more specifically the putamen, and hemorrhages in the subcortical white matter.[103–108] The MRI studies have indicated that damage in this region is due to local cellular edema.[109] This is apparently due to failure of the Na–K ATPase pump caused by the inhibition of cytochrome oxidase by formic acid.[109]

A number of mechanisms have been proposed to account for the specificity of the damage to the putamen. Putamen injury may be caused by both a high local concentration of formic acid potentiated by poor venous drainage in the lenticular nucleus from the veins of Rosenthal,[102] or inadequate arterial flow.[110] Specific metabolic vulnerability of the putamen may mean that it is more sensitive to the histotoxic hypoxia caused by formic acid accumulation. This region is known to have relatively higher rates of oxygen and glucose consumption than the adjacent white matter or other basal ganglia.[111] The effects of changing hemodynamics such as arterial hypotension and ischemia may also target this specific region,[112] although damage is still seen in the absence of marked hypotension or hypoxia, which suggests it is due to the direct effect of formic acid.[108] Hyperammonemia has also been associated with methanol poisoning[113] and this has been shown in MRI studies to affect the intensity of signals from the basal ganglia. It may have a possible role in the CNS toxicity of methanol poisonings.[103] Some of the hemorrhagic damage to the putamen may follow heparinization during hemodialysis, although hemorrhage has been seen in the absence of this treatment.[114–116]

Subcortical white matter is also affected during methanol poisoning. Sharpe et al.[89] suggest that changes in white matter, similar to those on the optic nerve, are caused by histotoxic hypoxia and breakdown of myelin sheaths. White matter lesions have the morphological characteristics of infarction due to circulatory stasis.[108] These affected areas are known as vascular watersheds and are more susceptible to histotoxic hypoxia, systemic hypotension, and metabolic acidosis, and include the subcortical white matter and the retrolaminar portion of the optic nerve.[117]

FEATURES

Clinical Features

Symptoms and signs of methanol intoxication usually are limited to the CNS, eyes, and gastrointestinal tract. Methanol poisoning typically involves mild CNS depression followed by a latent period lasting approximately 12–24 hours, depending in part on the methanol dose.[118] Consequently, the absence of symptoms and the presence of a clear sensorium do not exclude serious methanol poisoning.[81] The presence of blurred vision with a relatively clear sensorium strongly suggests the diagnosis of methanol poisoning.[81] The co-ingestion of ethanol typically delays the onset of symptoms beyond 24 hours. In a series of 323 patients ingesting methanol-

contaminated bootleg whiskey, the latent period averaged about 24 hours with a range of 40 minutes to 72 hours.[81] In this large series, several patients developed visual disturbances within 6 hours after the ingestion of adulterated moonshine including one patient with the onset of sudden amblyopia within 40 minutes. The length of the latent period is not a prognostic factor for the severity of methanol intoxication.[119] Following the latent period an uncompensated metabolic acidosis and visual dysfunction develop. Common symptoms associated with visual disturbances include headache, lightheadedness, nausea, vomiting, abdominal pain, and dyspnea.[8] Nystagmus rarely is associated with methanol poisoning. In a case series of 82 adults with methanol poisoning, only three patients had clinical evidence of nystagmus.[118] The presence of an unresponsive, dilated pupil indicates either major brain injury or dysfunction of the major visual pathways with a high risk of permanent loss of vision.[91] Gastrointestinal symptoms may be prominent as a result of the development of pancreatitis.[81] Bradycardia, shock, prolonged coma, seizures, persistent acidosis, and anuria are serious prognostic signs. During epidemics of methanol intoxication, death usually results from respiratory failure and sudden respiratory arrest.[81]

Central Nervous System

Headache, vertigo, lethargy, and confusion occur commonly in mild to moderate methanol intoxication. Methanol produces little euphoria compared with ethanol. The occurrence of coma and convulsions during severe cases of methanol poisoning suggests the presence of cerebral edema.[5] In addition to blindness, survivors of severe methanol intoxication may develop a Parkinsonlike extrapyramidal syndrome characterized by rigidity, bradykinesia, mild tremor, masked faces, lethargy, and mild dementia.[120,121] These clinical effects usually are associated with radiographic evidence of necrosis in the putamen and subcortical white matter. Other rare neurological complications of severe methanol intoxication include transverse myelitis,[108] cognitive deficits,[122] and pseudobulbar palsy.[119] These neurological abnormalities can occur in the absence of documented hypoxia and hypotension.

Vision

The ophthalmologic symptoms and signs of methanol poisoning range from blurred vision and altered visual fields to complete blindness. Blurred vision, decreased visual acuity, photophobia, and "feeling of being in a snow field" were common complaints in over one half of patients in an epidemic of methanol poisoning.[6] Most patients with methanol intoxication have some clinical evidence of ophthalmologic abnormalities, even in the absence of visual dysfunction.[91] Early signs of methanol intoxication are hyperemia of the optic disc and reduced pupillary responses to light.[123] Peripapillary retinal edema and edema of the optic disc with loss of physiological cupping develop more slowly than hyperemia of the optic disc. Concentric contraction of the visual field often occurs with central scotomas.[124] The extent of pupillary impairment and retinal edema correlates with the severity of the methanol intoxication. In a series of 323 patients ingesting methanol-contaminated whiskey, all 115 patients with systemic acidosis had visual impairment.[81] Other ocular signs included constricted visual fields, fixed and dilated pupils, and retinal edema. Within a day a white striated edema extends into the retina. Typically, the hyperemia of the optic disc subsides within 3 days, but the surrounding retinal edema may persist for several weeks. Case series indicate that most patients recover normal visual function,[125] but permanent visual sequelae occur in up to 25–33% of patients in epidemics of methanol intoxication.[6,119] Visual abnormalities usually do not develop when the ocular examination remains normal after the latent period for methanol intoxication.[126] Permanent ocular sequelae of methanol intoxication include diminished pupillary reactions to light, optic atrophy, optic cupping, peripheral constriction of the visual fields, central scotoma, reduced visual acuity, loss of color vision, and blindness.[81,91,127] Blindness is usually permanent, however, some recovery of visual function may occur within several months after methanol ingestion.[128]

Gastrointestinal Tract

Methanol typically produces nausea, vomiting, and abdominal pain. Abdominal pain may be severe as a result of the development of pancreatitis, but the absence of gastrointestinal symptoms does not rule out serious toxicity.[81] Acute pancreatitis as defined by elevated serum amylase is a common complication of severe methanol poisoning.[6] Elevation of hepatic aminotransferases usually is mild and transient.

Kidney

The occurrence of myoglobinuria is a rare complication of methanol poisoning. However, the presence of myoglobinuria may cause renal dysfunction. A patient

with an admission methanol concentration of 400 mg/dL developed acute renal failure in association with myoglobinuria.[129] Renal dysfunction peaked on the eighth hospital day and returned to normal within one month.

Laboratory Features

Acid–Base Disturbances

The presence of severe metabolic acidosis with increased anion and osmolar gaps strongly suggests the presence of methanol or ethylene glycol intoxication. However, certain clinical conditions also may produce similar laboratory abnormalities. Examples include diabetic ketoacidosis, alcoholic ketoacidosis, multiple organ failure, chronic renal failure, and critical illness.[130–132]

Differential Diagnosis and Using the Osmolal Gap

Osmolarity (osmoles per liter of solution) and osmolality (osmoles per kilogram solvent) are measures of the number of particles dissolved in solution.[133] The osmolal gap is a rapid approximation of the unmeasured, osmotically active constituents in the serum based on the difference between the measured osmolality and the calculated osmolarity. In the physiologic state, there is an osmol gap of approximately 10 mOsm/kg H_2O. This gap consists primarily of calcium, calcium anions, proteins, and lipids. In healthy individuals, Eq. (1) estimates the serum osmolarity (O_C) based on the concentrations of sodium, glucose, and urea nitrogen (BUN) in SI units (mmol/L).

$$\text{Calculated osmolarity}(O_C) = (1.86[\text{Na}] + [\text{BUN}] + [\text{glucose}]) \div 0.93 \quad (1)$$

The concentration units in Eq (1) are mEq/L or mOsm/L. To use traditional units divide the BUN concentration in mg/dL by 2.8 and the glucose concentration in mg/dL by 18. The measured osmolality (O_M) as reported by most clinical laboratories normally is about 270–290 mOsm/kg H_2O. Osmolarity or osmolality should be measured by the *freezing point depression* method because the vapor pressure method underestimates the contribution of volatile alcohols such as ethanol, isopropanol, methanol, propylene glycol.[134,135] The difference between the measured osmolality (O_M) and the calculated osmolarity (O_C) is the osmolal gap (O_G) as defined by Eq (2). A significant O_G is one greater than 10–15 mOsm/kg H_2O. The reference range for the O_G depends on the variability of the laboratory equipment for the four measurements involved in calculating the O_G, and the exact reference range of each measurement is specific to an individual hospital.[136] The presence of an elevated O_G suggests the presence of significant concentrations of ethylene glycol, propylene glycol, methanol, ethanol, isopropanol, or acetone. However, the absence of an elevated osmol gap does not rule out the presence of a significant concentration of methanol.

$$\text{Osmolal gap}(O_G) = O_M - O_C \quad (2)$$

The ingestion of methanol may produce a significant osmolal gap (O_G). For each milligram of methanol per deciliter, the O_G rises by about 0.34 mOsm/kg. A methanol concentration of 50 mg/dL (500 mg/L) raises the O_G by 17 mOsm/kg H_2O. Other osmotically active alcohols include isopropanol, ethylene glycol, and ethanol. The maximum O_G occurs following the peak absorption of methanol, prior to metabolism. As methanol metabolism proceeds, the O_G decreases and the anion gap increases. Under normal circumstances laboratory variation, accuracy of formula, and differences in analytical techniques can account for an O_G up to 20 mOsm/kg H_2O.[137,138] However, early in the course of methanol poisoning the O_G usually exceeds 20 mOsm/kg H_2O, but late in the course, the O_G may be normal as toxic concentrations of formate develop during methanol metabolism. The contribution of methanol metabolites to the O_G is small. Formate is charged and electrically balanced by sodium, and therefore, formate does not contribute to the O_G late in the course of methanol poisoning.[139] Consequently, late in the course of methanol poisoning, the O_G does not reflect the severity of the poisoning and the absence of an O_G does not exclude methanol intoxication.[140,141]

Table 1

Approximate Osmolal Contribution of Some Alcohols and Ketones

Compound	Concentration (mg/L)	Osmolal Contribution (mOsm/kg H_2O)
Propylene glycol	1000 (13 mmol/L)	13
Ethylene glycol	1000 (16 mmol/L)	16
Isopropanol	1000 (17 mmol/L)	17
Acetone	1000 (18 mmol/L)	18
Ethanol	1000 (22 mmol/L)	22
Methanol	1000 (34 mmol/L)	34

Other compounds also contribute to the O_G (See Table 1). Ethanol consumption commonly occurs during methanol intoxication, and the presence of ethanol in the serum contributes to the O_G. An erroneously elevated O_G may result from the presence of one of the following in the blood: spurious hyponatremia secondary to hyperlipidemia or to hyperproteinemia, the presence of endogenous solutes (e.g., amino acids during end organ failure), alcoholic ketoacidosis,[142] sorbitol, diatrizoate (IVP dye), glycerin, fructose, propylene glycol, or mannitol.

A normal osmolal gap does not rule out methanol poisoning. In mild, but nevertheless clinically significant methanol poisoning, the osmolal gap may be insensitive. A serum methanol concentration is the preferred test.

Anion Gap and Metabolic Acidosis

The plasma is in a state of electrical neutrality with the concentration of cations being equal to the concentration of anions. The anion gap is the difference between the sum of the measured cations and the sum of the measured anions. Under normal circumstances, this gap represents negatively charged proteins (albumin), fatty acids, and inorganic anions (sulfates, phosphates). Routinely, laboratories measure sodium and potassium, which together account for about 95% of the extracellular cations, as well as chloride and bicarbonate, which together represent about 85% of the extracellular anions. Normally, the anion gap is about 12–16 mmol/L, but the actual concentrations vary between laboratories depending on the accuracy of laboratory measurements. The generation of formate and, to a lesser extent, lactate contributes to the anion gap during methanol intoxication.[55,83] A significant anion gap may not be present early in the course of methanol intoxication when the serum bicarbonate concentration falls while the serum chloride concentration increases. Hence, a metabolic acidosis begins before the anion gap develops, but as the metabolism of methanol continues, an anion gap and a metabolic acidosis occur together. Equation (3) defines the anion gap.

$$\text{Anion Gap(AG)} = [(Na^+ + K^+) - (HCO_3^- + Cl^-)] \quad (3)$$

A profound metabolic acidosis occurs during severe methanol poisoning. Most seriously intoxicated patients with a serum bicarbonate level <18 mEq/L had serum methanol concentrations over 50 mg/dL (500 mg/L).[6] All symptomatic patients should have the arterial pH measured. Mortality correlates best with severity of acidosis and formate concentration rather than with serum methanol concentrations. In cases of methanol intoxication without metabolic acidosis, visual dysfunction usually does not develop.[91] Formate accounts for up to 50% of the early bicarbonate deficit.[143,144] In a patient with a maximum serum methanol concentration of 143 mg/dL (1430 mg/L), formate accounted for 42% of the increase in the anion gap in admission blood samples.[61] In later stages of methanol intoxication, lactate accumulates in the serum as a result of the formate-induced inhibition of mitochondrial respiration.[75] Clinical symptoms correlate more closely to metabolic acidosis rather than to serum methanol concentrations.[145] Endogenous formation of formate generally is <1.2 mg/dL (<12 mg/L).[146] Case series suggest that visual dysfunction occurs when formate concentrations exceed 20–30 mg/dL (200–300 mg/L).[75,90,147] Poor prognostic indicators include serum formate concentrations >50 mg/dL (>500 mg/L),[80,143] a pH <7.0, and coma or seizures on admission to the emergency department.[24]

Hematological and Biochemical Abnormalities

Routine laboratory examinations for serious toxicity include serum methanol and ethanol concentrations; serum electrolytes with calculation of anion and osmolar gaps; serum calcium; complete blood count; serum blood urea nitrogen, and creatinine; urinalysis; serum osmolarity; hepatic aminotransferase enzymes, serum amylase and serum creatine kinase. Isoamylase analysis indicates that a substantial portion of the amylase elevation may result from inflammation of the salivary glands, and therefore, the presence of an elevated serum amylase does not necessarily imply the presence of pancreatitis.[148] Case reports indicate that myoglobinuric renal failure may complicate methanol poisoning.[129] Pancreatitis, including severe necrotizing pancreatitis, is a common complication of severe methanol intoxication. In a series of 22 cases of methanol intoxication, 11 patients developed evidence of pancreatic damage and 1 patient died of acute necrotizing pancreatitis.[149] Elevation of the mean corpuscular volume occurs during severe methanol poisoning, probably as a result of generalized cellular swelling.[6] The hemoglobin, hematocrit, and leukocyte counts usually are normal.

Imaging Studies

The most consistent radiographic finding following severe methanol intoxication is bilateral necrosis of the putamen. In cases of severe methanol intoxication producing coma, nonenhanced CT at the time of admission can demonstrate hypodensity in the putamen, and less often, in the caudate nucleus.[105,109] However, CT imaging of the brain frequently is normal when

performed within the first 24 hours after methanol ingestion.[104,106] The necrosis of structures in the basal ganglia usually is not hemorrhagic. Although case reports of methanol intoxication associate putamen necrosis on CT scan with a permanent parkinsonianlike syndrome,[120] lesions in the basal ganglia on imaging studies do not necessarily correlate with clinical outcome.[114] Case reports suggest that permanent extrapyramidal dysfunction is unlikely when resolution of putamen lesions on MRI scans occurs within one month after methanol intoxication.[112] Bilateral necrosis of the putamen is not specific for methanol intoxication. Other causes of bilateral putamen changes include Wilson's disease, familial neurodegenerative disorders, Leber's optic atrophy, Leigh's disease (subacute necrotizing encephalomyelopathy), and hypoxic/ischemic injury.

Although initial MRI scans may not demonstrate optic abnormalities despite the presence of blindness on clinical examination, case reports indicate that repeat MRI scans one month after methanol poisoning demonstrate atrophy of the optic chiasm and prechiasmatic optic nerves.[150] The persistence of occipital lesions in the cerebral cortex on MRI scans suggests that visual impairment is permanent.[112] Other common findings of methanol poisoning on CT and MRI scans include cerebral edema and lesions of subcortical white matter, particularly in the frontal, occipital, and parietal lobes.[151] The peripheral components of hemispheric white matter usually remain unaffected.[152] Marked cerebral edema during severe methanol intoxication may cause attenuation of the ventricular system and brain stem herniation.[153] Uncommon radiographic abnormalities associated with methanol intoxication include bilateral symmetric pontine tegmental necrosis,[109] cerebellar necrosis,[104,154] and subarachnoid hemorrhage.[153] Brain hemorrhage is a rare complication of methanol poisoning.[116]

Electrophysiological Tests

On the ERG the negative *a*-wave reflects photoreceptor activity and the *b*-wave reflects the conduction of impulses through the bipolar cell layer including Muller glial cells. A reduction of the *a*- and *b*-wave amplitude occurs during acute and chronic methanol intoxication.[125,155] Reversible retinal and optic nerve dysfunction can occur during the early stage of methanol poisoning.[90] In two patients with transient visual dysfunction, the ERG and the VEP returned to normal about one month after methanol intoxication.[94] The VEP assess the visual pathways of the brain using either a flash or pattern recognition. The simultaneous recording of a flash ERG and flash VEP assesses retinal and optic nerve functions in uncooperative patients or patients with gross visual impairment. The wave I on the flash VEP is synchronized with the *b*-wave on the ERG. Although the wave I provides information on retinal function, examination of VEP results in a series of 19 methanol intoxications indicated that a normal wave I on VEP does not exclude retinal pathology.[93] Similarly, the presence of a normal wave III did not exclude the development of optic neuropathy. The presence of abnormal wave III morphology on flash VEP in a patient, who was not deeply comatose, suggested the probable development of optic neuropathy.

Interpretation of Serum Methanol Concentrations

A variety of factors complicate the correlation of serum methanol concentrations to clinical effects including differences in sample timing, individual variation, concentration of toxic metabolites, and the ingestion of ethanol. Clinical symptoms and mortality correlate more closely with metabolic acidosis rather than with serum methanol concentrations.[52] Consequently, the clinical presentation and outcome of two patients with the same serum methanol concentrations may be substantially different.[156] Small concentrations of methanol are present in fruits, vegetables, grape- and fruit-distilled spirits, and aspartame-containing beverages. Additionally, the methyltransferase and demethylase enzyme systems endogenously produce methanol from compounds, such as pectin.[157] The screening of blood samples from emergency department patients ingesting ethanol indicates that endogenous methanol production produces detectable methanol concentrations in some patients. In a series of 687 sequential emergency department admissions screened for alcohols by gas chromatography, 18 patients had methanol concentrations ranging from 2.3–4.0 mg/dL (23–40 mg/L).[158] The mean methanol concentration in blood samples from 519 Swedish drivers suspected of driving under the influence of ethanol was 7.3 mg/dL (73 mg/L) with a range of 1–23 mg/dL (10–230 mg/L).[159] The mean methanol concentration in 24, 1-year-old infants fed 100 mg aspartame/kg body weight was approximately 1 mg/dL (10 mg/L).[160] Peak methanol concentrations below 20 mg/dL (200 mg/L) usually are associated with asymptomatic individuals, but interpretation of the methanol concentration requires consideration of the

time since ingestion, the co-ingestion of ethanol and the acid–base status.[6] Peak methanol concentrations over 50 mg/dL (500 mg/L) indicate serious poisoning, particularly if an anion gap metabolic acidosis is present. Co-ingestion of ethanol reduces toxicity associated with a specific methanol concentration and delays the expression of signs and symptoms that are consistent with methanol exposure.[161]

MANAGEMENT

Priorities

Management priorities depend upon the circumstance of presentation and are shown in Fig. 2. When a patient presents soon after the possible ingestion of a methanol containing product, the first priority is to assess the likelihood and magnitude of ingestion, inhibit methanol

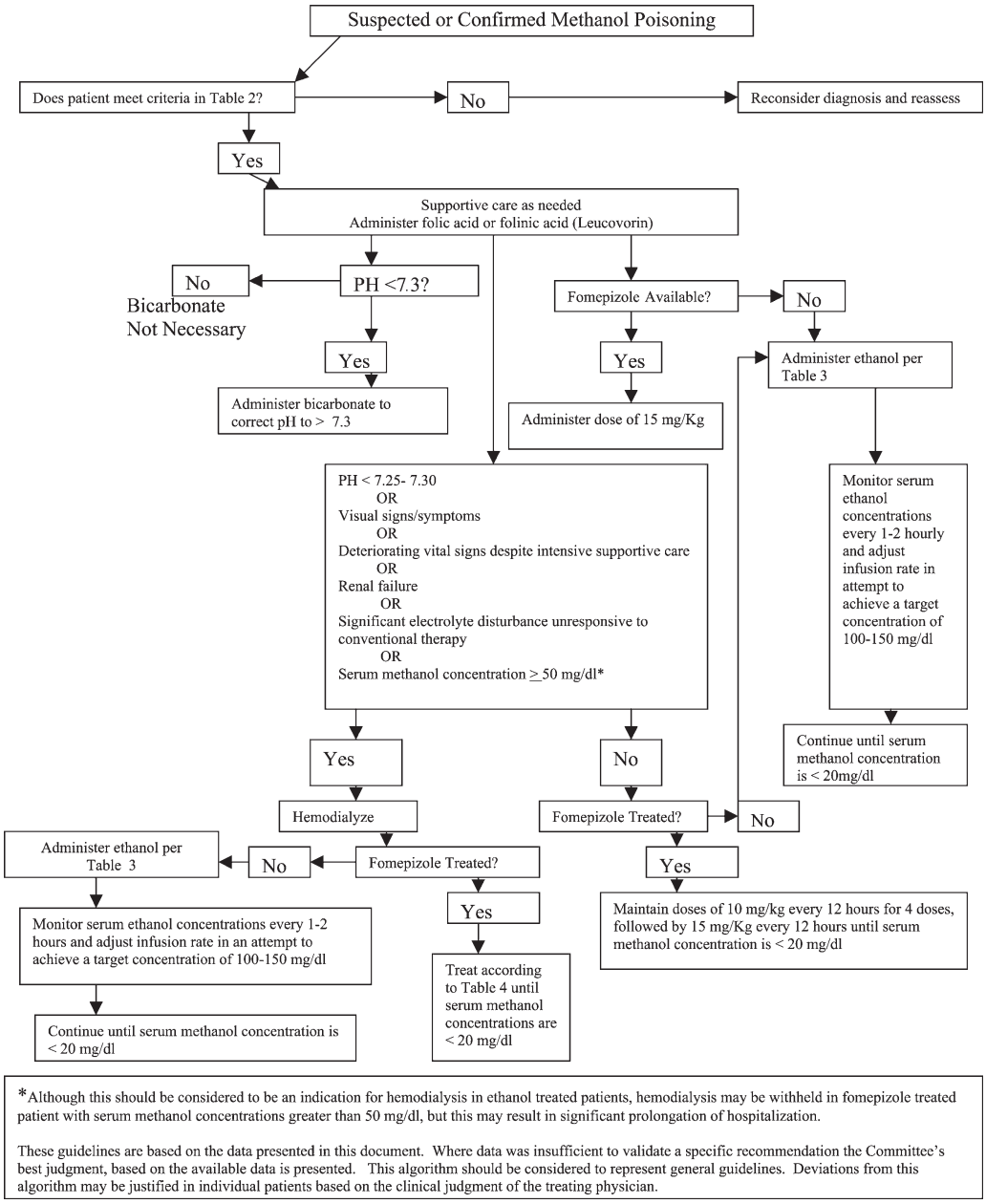

Figure 2. Management priorities for methanol poisoning.

metabolism if ingestion is likely, and then proceed to confirm and quantify the serum methanol concentration. When an individual presents following ingestion of methanol and ethanol together, inhibition of methanol metabolism is likely and acidosis is unlikely. The first priority is to assess the serum ethanol concentration, determine if acidosis is present, and to quantify the presence of methanol. In either case, once the serum methanol concentration has been determined or estimated by the osmolal gap, plans can be made for further inhibition of metabolism or for enhanced elimination. Hemodialysis solely to shorten the time of hospitalization should not be considered emergent.

If a patient presents with ophthalmological symptoms and signs or with significant acidosis in the context of a likely methanol ingestion, the initial priorities are to correct the acidosis with sodium bicarbonate, attempt to enhance metabolism of formate to CO_2 by administration of folinic acid, inhibit further metabolism of methanol to formate with either fomepizole or ethanol, and finally to arrange hemodialysis for further correction of metabolic abnormalities, if necessary. Initiation of this sequence should not wait for serum methanol quantification. Enhanced elimination of methanol in this situation is a secondary benefit of emergent hemodialysis for management of acute toxicity, not the primary goal. If the acidosis corrects rapidly prior to hemodialysis and it is determined that no methanol remains, hemodialysis may be unnecessary.

Stabilization and Supportive Care

The initial evaluation should be directed toward the evaluation and correction of immediate life-threatening complications to the airway, breathing, and circulation. The most common serious complications of methanol poisoning are metabolic acidosis, ophthalmologic abnormalities, and coma. Initial management, therefore, is focused on preventing the development of these complications, if they have not already supervened, or correcting the acid–base disturbance if present.

In patients with normal renal function, intravenous fluids should be administered in adequate volumes to maintain urine output and the patient should be monitored carefully to detect evidence of early renal failure.

Seizures, though rare, should be treated with standard doses of benzodiazepines such as diazepam or lorazepam.

Frequently, patients who ingest methanol are also ethanol abusers. These patients should receive thiamine 100 mg intravenously as well as multivitamin supplementation.

Investigations to Guide Management

Laboratory tests for all patients who ingest potentially toxic amounts of methanol include the following: blood count, electrolytes, urinalysis, arterial blood gases, serum calcium, lipase, amylase, creatine kinase, and osmolality as well as serum methanol and ethanol concentrations. A CT scan or MRI of the head is indicated for patients with altered mental status, seizure, or focal neurologic abnormalities.

Gastrointestinal Decontamination

Methanol is absorbed rapidly and even if gastrointestinal decontamination techniques were effective, there would be little opportunity to prevent its absorption. There are no clinical or human in vivo studies that examine the efficacy of gastrointestinal decontamination in actual or simulated methanol poisoning cases. Standard recommendations that advocate the use of gastric lavage[72,162] and the generic intervention of "gastric decontamination"[163] prevail in the contemporary literature, but without any evidence to support their use. Ipecac syrup-induced emesis has been condemned by some for use in methanol poisoning due to the risk of aspiration of gastric contents by an obtunded patient[72,162] and universally as being ineffective with regard to improving patient outcomes.[164] Activated charcoal administration is discouraged generally due to the supposition that methanol is not adsorbed by activated charcoal.[165] However, two studies, one in vivo[166] and one in vitro,[167] suggest that there may be merit to the use of activated charcoal. Nevertheless, a plethora of methodological limitations makes extrapolation of these data unreliable. Furthermore, ethanol-activated charcoal research is sometimes applied to the methanol-poisoned patient.[168–170] However, any inference about the use of activated charcoal in methanol-poisoned patients that is based on ethanol-activated charcoal research is not applicable. Therefore, activated charcoal is not recommended. On the other hand, if a toxic amount of a substance that is known to be adsorbed by activated charcoal has been taken in conjunction with methanol, activated charcoal administration should be encouraged. For a detailed review of the activated charcoal alcohol literature please refer to the Appendix.

Correction of Metabolic Disturbances

The degree of acidosis at presentation most consistently correlates with severity and outcome.[2,24,52,81,143,171] A pH below 7.3 should be treated with intravenous sodium bicarbonate solution to correct the acidosis to the normal range (7.35–7.45). High doses may be required to achieve correction, particularly if alcohol dehydrogenase has not yet been inhibited and formic acid production is ongoing.[75] Adding bicarbonate to the dialysate during hemodialysis also may help restore the serum bicarbonate concentration, but efforts to correct acidosis should not wait for dialysis.

Correction of the acidosis reduces the ratio of formic acid to formate.[50] Compared with formate, undissociated formic acid is three times more potent as an inhibitor of mitochondrial cytochrome oxidase, the final step in mitochondrial electron transport.[50] The resultant anaerobic glycolysis produces a lactic acidosis that contributes significantly to the late acidosis associated with severe methanol poisoning and further increases the ratio of formic acid to formate.[50,75] In this context, it is not surprising that coma and seizures have been linked with severity of acidosis.[24,119] These symptoms may simply reflect the cerebral metabolic impact of formic acid and lactate.

Thus improvement in acidosis not only corrects general acid–base balance, but likely impacts specific pathophysiology to improve outcome. Limited patient data support this as well. In anecdotal reports from early large series, authors noted dramatic improvement with correction of acidosis, particularly of ophthalmologic symptoms.[81,118] In a report of 28 patients suffering methanol exposure in New Guinea, 17 had clear signs of acidosis[119] as they were treated solely with bicarbonate. Only four died and eight had disabling sequelae including blindness, visual impairment, and pseudobulbar palsy, but the rest had complete recovery.[119] These outcome data are similar to some other series that included management with ADH blockade and hemodialysis,[2,143] but not others.[52,53] Inadequate characterization of all patients at time of presentation prevents a rigorous comparison. More recently, in a series of patients treated with a combination of therapies, Liu[24] found that patients experiencing complete recovery of vision had more rapid correction of acidosis that those who did not.

Amelioration of acidosis may also enhance formate elimination. In a single case report of a patient treated only with bicarbonate for the first 12 hours after presentation, serial methanol and formate concentrations demonstrated that formate elimination increased with correction of the pH, before other specific therapies were initiated.[61]

Inhibition of Methanol Metabolism by Ethanol and Fomepizole

Rationale for the Use of Ethanol and Fomepizole

Ethanol has approximately 10 times greater affinity for alcohol dehydrogenase than does methanol.[170] Therefore, ethanol competitively inhibits the metabolism of methanol to its toxic metabolite, formate, by occupying the receptor sites of alcohol dehydrogenase. Fomepizole has been shown to be a potent inhibitor of alcohol dehydrogenase in the monkey[172] and in man.[173] A plasma fomepizole concentration of 0.8 mg/L inhibits alcohol dehydrogenase activity in monkeys.[172]

If administered soon after exposure, ethanol and fomepizole should prevent, or at least reduce, the further formation of toxic metabolites. This inhibition of hepatic metabolism, results in a substantially decreased elimination rate of methanol. For example, in a series of four cases of methanol intoxication with initial methanol concentrations ranging from 31–135 mg/dL (310–1350 mg/L), the median elimination half-life of methanol during ethanol therapy was 43.1 hours (range 30.3–52.0 hours).[34] Case reports suggest that ethanol prevents ophthalmologic abnormalities and anion-gap metabolic acidosis in patients who present with a normal pH and high concentrations of ethanol and methanol.[82,174]

Although ethanol has been used as an antidote for methanol poisoning since the 1940s,[118] it does not have regulatory approval from the United States. Food and drug administration (FDA) for this condition. Despite the frequent use of ethanol to treat methanol poisoning, there are no prospective studies that validate the administration of ethanol as a means of improving clinical outcome.

If administered early after dosing, fomepizole has been demonstrated to prevent metabolic acidosis and ocular toxicity associated with methanol poisoning in animals.[172,175–178] Data on 32 patients poisoned with methanol and treated with fomepizole have been published. Of them 11 were part of a prospective case series,[53] 14 were part of a retrospective case series,[179] and 7 were case reports.[180–185] However, it has yet to be confirmed that clinical outcome is improved by the use of fomepizole.

Indications for the Use of Ethanol and Fomepizole

Ethanol or fomepizole should be administered *as soon as possible* after methanol ingestion in order to prevent the production of formate. Proposed indications for the use of ethanol and fomepizole are listed in Table 2. It should be understood that there are inadequate data on the exact serum methanol concentration at which the use of ethanol or fomepizole is necessary to prevent ophthalmological damage. The recommendations given are based on limited clinical data and general consensus.

There are no clinical data to confirm the superiority of fomepizole over ethanol in the treatment of adult or pediatric methanol poisonings. The primary disadvantages of the use of fomepizole are the high acquisition cost and the limited clinical experience of its use.

However, the administration of fomepizole may be preferred to ethanol for patients with methanol poisoning for many reasons. It is easier to administer than ethanol and has a longer duration of action. Ethanol dosing is complex with an increased risk for prescription, formulation, and administration errors. Fomepizole does not cause CNS depression, and thus will not confuse the evaluation of a patient who has ingested other substances with CNS depressant activity. From the nursing perspective, fomepizole's 12-hour dosing schedule is less labor intensive compared with a continuous IV infusion or an hourly oral dosing schedule of ethanol. Thus, the administration of fomepizole does not require critical care support. It also requires less laboratory support than that used to monitor ethanol administration. Fomepizole may be used in the presence of cautions to the use of ethanol. As there is a greater risk of children developing hypoglycemia during the administration of ethanol, the use of fomepizole instead of ethanol is a theoretical advantage. In addition, it would be preferable that pregnant patients in the first trimester did not receive ethanol because of concerns regarding the fetal alcohol syndrome. Fomepizole will not complicate the care of patients with a history of ethanol abuse. It does not reinforce dependence or provide satisfaction to those ingesting methanol as a means to receive ethanol. Fomepizole may be less injurious to veins compared to ethanol. This is a potential advantage in the treatment of methanol poisoning in young children.

Relative Contraindications to the Use of Ethanol and Fomepizole

Ethanol should be used with caution in patients who have also ingested drugs that produce CNS depression as the administration of ethanol would be expected to enhance the depressant effect of these drugs.

Flushing and hypotension may occur if ethanol is administered and the patient has also received disulfiram, metronidazole, or chlorpropamide. Ethanol should be used with caution in patients with hepatic disease and the oral administration of ethanol preferably should be avoided when there is a recent history of gastrointestinal ulcers.

Fomepizole should not be administered to patients with known hypersensitivity reactions to fomepizole or to other pyrazole compounds.

Table 2

Proposed Indications for the Treatment of Methanol Poisoning with Ethanol or Fomepizole

Criteria
Documented plasma methanol concentration >20 mg/dL (>200 mg/L)[53]
Or
Documented recent history of ingesting toxic amounts of methanol and osmolal gap >10 mOsm/kg H_2O[a]
Or
History or strong clinical suspicion of methanol poisoning *and* at least two of the following criteria:
(A) Arterial pH <7.3
(B) Serum bicarbonate <20 meq/L(mmol/L)
(C) Osmolal gap >10 mOsm/kg H_2O[a]

[a] Laboratory analysis by freezing point depression method only.

Ethanol Pharmacokinetics, Dose, Administration, and Adverse Effects

Ethanol Pharmacokinetics

Ethanol is absorbed rapidly from the gastrointestinal tract, primarily from the duodenum. Factors that prolong gastric emptying, including the presence and type of food, reduce and delay ethanol absorption. Ethanol distributes into the total body water with an approximate volume of distribution of 0.6–0.7 L/kg. Ethanol rapidly crosses the placenta and the blood–brain barrier. The liver metabolizes 90–98% of an absorbed dose of ethanol, while the kidneys and lungs excrete most of the remaining dose of ethanol unchanged. Zero-order kinetics characterize the hepatic metabolism of ethanol except at very low (<10–20 mg/dL; <100–200 mg/L) or very high (>200–300 mg/dL; >2000–3000 mg/L) concentrations.[186,187] Typical ethanol elimination rates average about 15–20 mg/dL/h (150–200 mg/L/h) in

healthy adults with a range 10–34 mg/dL/h (100–340 mg/L/h).[188] The ethanol elimination rate usually is higher in ethanol abusers compared with nonethanol abusing adults.

Ethanol Dose

The loading dose of ethanol is 600–800 mg/kg (0.6–0.8 g/kg). Initially the serum ethanol concentration should be monitored every 1–2 hours in order to ensure that the serum concentration remains in the recommended therapeutic range of approximately 100–150 mg/dL.[118,189] This is based on empiric recommendations from clinical experience during the 1940s rather than from scientifically derived dose-response data.[52,190] There are limited data on the minimum concentration of ethanol necessary to block the formation of formate. Although clinical experience suggests that ethanol concentrations <100 mg/dL (1000 mg/L) are effective,[52] case reports indicated that some metabolism of methanol to formate occurs when the serum ethanol concentration falls below 100 mg/dL (1000 mg/L) during treatment for methanol intoxication.[90] At methanol concentrations as low as 1–2 mg/dL (10–20 mg/dL), experimental data indicate that methanol metabolism occurs when the blood ethanol concentrations falls below 20–30 mg/dL (200–300 mg/L).[36]

In a study of 20 ethanol abuse patients admitted for detoxification, analysis of blood samples demonstrated a mean methanol concentration of 1.15 mg/dL (11.5 mg/L) and a range 0.16–2.8 mg/dL (1.6–28 mg/L).[38] Whole blood methanol concentrations remained constant until the blood ethanol concentrations decreased below 30 mg/dL (300 mg/L). Theoretically, the amount of ethanol necessary to prevent the formation of toxic metabolites depends on the amount of methanol present and, therefore, relatively higher doses of ethanol may be required for very large ingestions of methanol. The average maintenance dose is about 110 mg ethanol/kg/h (1.4 mL 10% ethanol/kg/h).[189] The actual dose varies from 66 mg ethanol/kg/h (0.8 mL 10% ethanol/kg/h) for nondrinkers to 154 mg ethanol/kg/h (2.0 mL 10% ethanol/kg/h) for ethanol abusers as outlined in Table 3.[189]

For severe adult poisoning in which medical care will be delayed several hours, the use of approximately four 1-oz oral doses of 80-proof whiskey before or during transport to the hospital is an option [See Eq. (4)].

$$\text{Oral loading dose} = \text{grams ethanol/mL 80 proof solution} \quad (4)$$

Goal: Serum ethanol concentrations of 100 mg/dL (1000 mg/L)

Assuming: Volume of distribution (V_d) of ethanol is 0.6 L/kg

Loading dose (grams ethanol) for 70 kg patient $= 1$ g/L $\times$ 0.6 L/kg $\times$ 70 kg $= 42$ g

Assuming: 80 proof solution $= 40\%$ ethanol and specific gravity $= 0.79$ g/mL

Amount (grams) ethanol in 80 proof solution $= 0.40$ v/v ethanol; $= 0.40 \times 0.79$; $= 31.6$ g/100 mL

Amount of 80% proof solution required = Loading dose $= 42$ g; $= 42.0$ g $\div$ amount ethanol in 80 proof solution; $= 42$ g $\div$ 31.6 g per 100 mL 80 proof solution; $= 132.9$ mL (or about 2 mL/kg body weight).

Table 3

Recommended Therapeutic Doses of Ethanol Based on Average Pharmacokinetic Values

	Amount Absolute Ethanol[a]	Volume (43% Oral Solution)[b]	Volume (10% IV Solution)[c]
Loading dose[d]	600 mg/kg	1.8 mL/kg	7.6 mL/kg
Standard maintenance dose (nondrinker)	66 mg/kg/h	0.2 mL/kg/h	0.83 mL/kg/h
Standard maintenance dose (ethanol abuser)	154 mg/kg/h	0.46 mL/kg/h	1.96 mL/kg/h
Maintenance dose during dialysis (nondrinker)	169 mg/kg/h	0.5 mL/kg/h	2.13 mL/kg/h
Maintenance dose during dialysis (ethanol abuser)	257 mg/kg/h	0.77 mL/kg/h	3.26 mL/kg/h

There is considerable variability of ethanol elimination from patient to patient. Therefore, these dosing recommendations should be considered as an initial guide. Close monitoring of serum ethanol concentrations is essential in order to achieve a value within the recommended range.

[a] Specific gravity = 0.79.

[b] Equivalent to 86 proof undiluted liquor (34 g ethanol/dL).

[c] Equivalent to 7.9 g ethanol/dL.

[d] Assumes initial ethanol concentration is zero, dose is independent of chronic drinking status. (Adapted from McCoy et al.[189]).

Ethanol therapy should continue until the serum methanol concentration is <20 mg/dL (200 mg/L) and the patient is asymptomatic with a normal arterial pH. In a study of 46 patients during an epidemic of methanol poisoning at a Michigan state prison, no complications developed in these patients when the ethanol infusion was stopped at methanol concentrations $<20-30$ mg/dL ($<200-300$ mg/L).[6] The presence of a metabolic acidosis despite methanol concentrations <20 mg/dL (<200 mg/L) suggests the presence of substantial concentrations of formate or an alternate etiology for the acidosis.

Table 3 outlines the range of maintenance ethanol doses based on average pharmacokinetic values and the chronic use of ethanol. The dose for moderate ethanol drinkers is about the mean between the value listed for nondrinkers and the value for ethanol abusers listed in Table 3. The actual amount of ethanol administered depends on the results of frequent monitoring of the serum ethanol concentration. First-pass metabolism reduces the bioavailability of orally administered ethanol and the use of intravenous ethanol produces slightly higher and earlier peak serum ethanol concentrations compared with the oral route.[191] The clinical significance of these pharmacokinetic differences remains unclear. Low doses of ethanol, food, and chronic ethanol consumption increase first-pass metabolism.[192] This alteration is less than 10% following the administration of moderate doses of ethanol after a light meal.[193]

Ethanol Administration

For patients who have ingested ethanol in addition to methanol, the loading dose of ethanol should be reduced accordingly. Ethanol may cause orthostatic hypotension in patients who use vasodilator agents.

Ten percent (volume/volume) intravenous solutions of ethanol are no longer available commercially in the United States. If available, a 5% ethanol in dextrose 5% (D5A5) solution may be increased to 10% by removing 56 mL of fluid from 1 L of D5A5, and replacing the extracted fluid with 56 mL of 95% ethanol. Alternately, withdrawing 105 mL of fluid from 1 L of 5% dextrose and replacing the extracted fluid with 105 mL of 95% ethanol produces a 10% ethanol solution. If absolute alcohol is to be used, 53 mL of D5A5 should be extracted and replaced with 53 mL of absolute alcohol or 101 mL of D5W should be extracted and replaced with 101 mL of absolute alcohol to make 10% ethanol solutions. Prior to dilution, the ethanol should be purified through a micron filter because these solutions are not pyrogen-free. Denatured ethanol should not be used in the diluted solution. Ethanol may be administered orally as a 20% pharmaceutical preparation or as an alcoholic beverage.

The infusion of ethanol requires 1–2 hours monitoring of serum ethanol concentrations until the serum ethanol concentration is within the recommended range of 100–150 mg/dL (1000–1500 mg/L). Serum ethanol concentrations may change after the achievement of steady state concentrations and, therefore, the serum ethanol concentration should be monitored every 2–4 hours during this period. Young children also require frequent monitoring of serum glucose concentrations. Variability in individual metabolic rates and the rate-limited kinetics of ethanol may cause large changes in the serum ethanol concentration after only small alterations in the infusion rate. Consequently, any change in the infusion rate requires 1–2 hours monitoring of the serum ethanol concentration, until it reaches a steady state within the therapeutic range. Intravenous ethanol should be administered with an infusion pump and the patient should be monitored in an intensive care setting in order to observe for signs of CNS and respiratory depression and to monitor the serum ethanol concentration.

The kinetics of ethanol following oral administration is more unpredictable than after intravenous dosing. Therefore, close monitoring of serum ethanol concentrations also is necessary after oral loading doses and changes in the oral dosage. Because of the hyperosmolarity of loading doses of ethanol, the initial dose of ethanol is administered over 1 hour. To increase tolerability, the oral solution of ethanol is diluted to 20% and administered hourly via a nasogastric tube.

Use of Ethanol in Pregnant Patients

The treatment of methanol poisoning with ethanol is short-term, over several days. The adverse reproductive effects associated with ethanol are not expected to occur following the use of ethanol as an antidote for methanol poisoning during the second and third trimester. The use of any alcohol during the first trimester is more controversial because of the association of fetal alcohol syndrome with peak ethanol concentrations during a short period of vulnerability during organogenesis.

Use of Ethanol in Children

There are few data on the complications of the ethanol infusions in children. Children are more susceptible to the development of hypoglycemia during ethanol intoxication compared with adults.[194]

Adverse Effects of Ethanol

Ethanol may cause hypoglycemia, particularly in children and in malnourished patients. Administration of ethanol in methanol poisoning may produce clinical signs and symptoms of ethanol intoxication.

A 10% solution of ethanol is hyperosmolar (1713 mOsm/L) and, therefore, a local phlebitis may develop following the intravenous use of this solution. This is a particular concern in young children. The administration of 10% ethanol intravenously frequently requires central venous access.

Fomepizole Pharmacokinetics, Clinical Efficacy, Dose, Administration, and Adverse Effects

Fomepizole Pharmacokinetics

Fomepizole pharmacokinetic data are based on a small number of animal studies, human volunteer studies, and case reports. There are few data on the effect of age, gender, hepatic insufficiency, or renal dysfunction on the pharmacokinetics of fomepizole.

Fomepizole is absorbed rapidly by the oral route but is usually administered intravenously. It is distributed rapidly into the total body water with a volume distribution of approximately 0.6–1.0 L/kg. Ninety-seven percent of fomepizole elimination occurs by hepatic metabolism.[195] The major metabolite in humans is the inactive 4-carboxypyrazole accounting for approximately 80–85% of a therapeutic dose. Other minor, inactive metabolites include 4-hydroxymethylpyrazole and the *N*-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole. Only 1–3.5% of an administered dose of fomepizole appears unchanged in the urine of healthy volunteers.

The plasma elimination rate of fomepizole varies with dose and with duration of treatment. At plasma fomepizole concentrations of 8–25 mg/L, fomepizole displays dose-dependent, nonlinear elimination that does not match Michaelis–Menten kinetics. These complicated kinetics probably result from the action of multiple metabolizing enzymes, some of which are saturable and some of which are inducible. Fomepizole induces the P_{450} mixed function oxidase system, particularly P_{450} CYP2E1.[196] The elimination rate of fomepizole increases over the first 30–40 hours after the initial dose. Enzyme induction appears to be complete after this period, and first-order elimination of fomepizole then occurs. At therapeutic doses, the apparent rate of elimination is about 0.41 mg/L/h, and thus a dose of 10 mg/kg is eliminated in approximately 25 hours.[195]

Hemodialysis is often undertaken during fomepizole therapy and case reports indicate that hemodialysis removes substantial amounts of this antidote.[197,198] Although fomepizole removal by hemodialysis has not been studied in methanol poisoned patients, the removal rates were 50 and 83 mg/h in two patients with anuric renal failure due to ethylene glycol poisoning; the mean dialysances were 117 and 136 mL/min, respectively.[199] Studies using a pig model have confirmed that the dialysability of fomepizole is similar to that of urea.[200] In a study of healthy volunteers, the renal clearance of fomepizole was very low with only about 3% of a therapeutic dose excreted in the urine unchanged.[195] The renal clearance for a fomepizole dose of 10 and 20 mg/kg was 0.022 and 0.014 mL/min/kg, respectively.[195]

Clinical Efficacy of Fomepizole—Case Series

Brent et al.[53] reported a case series of 11 patients poisoned with methanol whose admission serum methanol concentrations ranged from 23 (230 mg/L) to 612 mg/dL (6120 mg/L). Serum formic acid concentrations were detectable in eight patients and these correlated very closely with the initial arterial pH values. Fomepizole was administered with a loading dose of 15 mg/kg followed by bolus doses of 10 mg/kg every 12 hours; after 48 hours the bolus doses were increased to 15 mg/kg 12-hourly to counteract the induction of fomepizole metabolism and continued until the serum methanol concentration was <20 mg/dL (<200 mg/L). The median duration of treatment with fomepizole was 30 hours (range 0.5–60 hours) and the patients received a median of four doses (range 1–10 doses). Plasma fomepizole concentrations were at or above 0.8 mg/L on all but three of 155 measurements. During treatment with fomepizole, plasma formic acid concentrations fell and metabolic abnormalities resolved in all patients. Seven of the eleven patients underwent hemodialysis after administration of the loading dose of fomepizole. Seven patients initially had ophthalmologic abnormalities but at the end of the trial no patient had decrements in visual acuity and two patients died from anoxic brain injury though this was present at the time fomepizole treatment was initiated. Methanol elimination in patients who did not undergo dialysis followed first order kinetics with a half-life of 54 hours.

Mégarbane et al.[179] reported a retrospective clinical study performed in three intensive care units in

university-affiliated teaching hospitals. Fourteen methanol-poisoned patients were treated with fomepizole between 1987–1999. The median plasma methanol concentration was 50 mg/dL (500 mg/L) with a range of 4–146 mg/dL (40–1460 mg/L). The median anion gap was 22.1 mmol/L with a range 11.8–42.2 mmol/L. The median arterial pH was 7.34 with a range 7.11–7.51, and the median and range of serum bicarbonate concentration was 17.5 and 3.0–25.0 mmol/L, respectively. Patients received oral or intravenous fomepizole until the blood methanol concentration was undetectable. The median and range of total fomepizole dose was 1250 and 500–6000 mg, respectively. The median number of twice-daily doses was 2 with a range of 1–16. Four patients with visual impairment present on admission underwent hemodialysis, and four patients with plasma methanol concentrations $\geq$ 50 mg/dL ($\geq$ 500 mg/L) treated without hemodialysis recovered fully. Patients without pre-treatment ophthalmologic disturbances recovered with no sequelae. There were no deaths. Analysis of methanol kinetics in five patients demonstrated that fomepizole was effective in blocking the metabolism of this poison. The authors concluded that fomepizole was safe and well tolerated, even in the case of prolonged treatment, and that if their results were confirmed in prospective studies, hemodialysis may prove unnecessary in patients poisoned with methanol who present without ophthalmologic impairment or severe acidosis.

Clinical Efficacy—Case Reports

Bekka et al.[184] reported a case of mixed methanol and isopropanol poisoning in a patient who declined dialysis but agreed to treatment with intravenous fomepizole. The patient was asymptomatic on arrival at hospital with initial blood methanol and isopropanol concentrations of 146 (1460 mg/L) and 390 mg/L, respectively. Blood ethanol was undetectable. The patient was treated with fomepizole 10 mg/kg intravenously 5 hours after his most recent ingestion of methanol-containing glass cleaner, together with folic acid 200 mg intravenously. This therapeutic combination was administered twice daily for eight days with the fomepizole dose being reduced from 10 to 5 mg/kg and then to 2.5 mg/kg on days seven and eight. The clinical course was uneventful. No metabolites of methanol or isopropanol were detected. The decay of plasma methanol concentrations was in keeping with first order kinetics. The elimination half-life of methanol was 47.6 hours. Serum fomepizole concentrations were not measured.

Brown et al.[185] reported the clinical course of a 5-year-old boy who ingested an unknown quantity of a 40% methanol-containing windshield washer fluid. He presented to the emergency department within 60 minutes of ingestion. He had no signs of intoxication and no apparent ophthalmologic abnormalities. His serum methanol concentration on admission was 35 mg/dL (350 mg/L). The osmolal gap was 36 mOsm/kg H_2O. He was transferred to a tertiary care facility, where on arrival he complained of intermittent abdominal pain, was slightly confused and tachypneic. His pH was 7.43 and his serum bicarbonate was 20 mEq/L. Eight hours after the ingestion, fomepizole 15 mg/kg was administered as an intravenous loading dose; 14 hours after the ingestion, the serum methanol concentration was 28 mg/dL (280 mg/L) and hemodialysis was started and continued for 4 hours until the methanol concentration was reduced to zero. Fomepizole therapy was discontinued. The child was discharged the following day, with no detected ophthalmologic abnormalities or other sequelae.

Burns et al.[180] administered fomepizole to a 32-year-old man with a history of ethanol abuse who had ingested a methanol-containing windshield washer fluid some 4 hours previously. On admission the patient was intoxicated, disorientated, and agitated. His pH was 7.41, his serum methanol concentration was 40 mg/dL (400 mg/L) and his serum ethanol concentration was 15 mg/dL (150 mg/L). Sedation, tracheal intubation, and mechanical ventilation were performed for increasing agitation and confusion. Intravenous folinic acid was administered in an initial dose of 50 mg and five additional intravenous doses of 50 mg were given at 4-hourly intervals. Fomepizole, 15 mg/kg, was given 6.5 hours after the methanol ingestion. Two additional intravenous 10 mg/kg doses of fomepizole were administered at 12-hourly intervals until the serum methanol concentration was $<$ 20 mg/dL ($<$ 200 mg/L). The serum fomepizole concentration ranged from 15.4 to 36.2 mg/L. The patient's visual acuity remained normal. During fomepizole monotherapy, the methanol elimination half-life was 70 hours, if a first order process is assumed. The methanol elimination rate was 2.8 mg/L/h if a zero order process is assumed.

A case of fatal methanol poisoning was reported by Girault et al.[181] The patient was a 35-year-old chronic alcohol abuser who was found by her husband in an inebriated state with blurred vision. On arrival at hospital several hours later, she was in deep coma with a GCS of 4 and bilateral fixed pupils. Shortly after admission, she had a generalized seizure and was intubated and mechanically ventilated. The serum methanol concen-

tration 1.5 hours after admission was 190 mg/dL (1900 mg/L). No ethanol was detected. Her pH was 6.92. She was treated with intravenous sodium bicarbonate and with fomepizole 10 mg/kg intravenously 3 hours after admission. Thereafter, 10 mg/kg of fomepizole was administered intravenously twice daily. Hemodialysis was initiated as well as folinic acid at a dose of 50 mg every 4 hours for 24 hours. Computerized tomography of her head performed 30 hours after admission demonstrated bilateral cerebral low-density images in the putamen, occipital, and parietal regions as well as diffuse cerebral edema. Brain death was determined.

Hantson et al.[182] reported two patients poisoned with methanol. The first, a 56-year-old man was referred to hospital 41 hours after ingesting methanol. Although he was conscious, he had visual impairment. His initial pH was 7.16 and the bicarbonate concentration was 4 mmol/L. The serum methanol concentration was 78 mg/dL (780 mg/L) and the formate concentration was 682 mg/L. The patient was treated with hemodialysis for 4 hours and sodium bicarbonate 540 mmol was administered together with ethanol 600 mg/kg, followed by a continuous infusion of ethanol 228 mg/kg/h over 8 hours. Folinic acid 50 mg 6-hourly was also given. The patient became stuporous during ethanol therapy and therefore, fomepizole 15 mg/kg was orally substituted. Fomepizole was first administered approximately 8-hours after admission. Overall, six 15 mg/kg doses of fomepizole were given orally at 12-hourly intervals. At the beginning of fomepizole therapy, the serum methanol and ethanol concentrations were 27 (270 mg/L) and 124 mg/dL (1240 mg/L), respectively. The serum formic acid concentration remained low during fomepizole therapy. The methanol half-life during ethanol therapy but after hemodialysis was 27.5 and 15.4 hours when the ethanol had disappeared from the blood. On discharge from hospital the patient had no disturbances of his vision.

The second patient reported by Hantson et al.[182] was an 18-year-old woman who was admitted 16 hours after ingesting methanol in a suicide attempt. On admission, she was conscious and agitated, and complained of disturbances in her vision. Her arterial pH was 7.19 and her serum bicarbonate was 6 mmol/L. The serum methanol concentration on admission was 49 mg/dL (490 mg/L) and the formic acid concentration was 901 mg/L. Ethanol therapy was started immediately at a dose of 600 mg/kg followed by 66 mg/kg/h. Eight hours after admission she complained of abdominal pain and diffuse tenderness was noted on examination of her abdomen. Ultrasound examination was consistent with a diagnosis of acute pancreatitis and computerized tomography of her abdomen confirmed the severity of pancreatic injury. Ethanol therapy was, therefore, stopped 12 hours after the beginning of the continuous infusion and fomepizole was commenced. At this time the blood methanol and ethanol concentrations were 32 (320 mg/L) and 186 mg/dL (1860 mg/L), respectively. Fomepizole was given orally in a dose of 15 mg/kg and three further doses of 10.8, 7.6, and 5.4 mg/kg were administered at 12-hours intervals. Intravenous folinic acid 50 mg every 6 hours was also prescribed. The half-life of methanol was 30 hours during fomepizole therapy and 12.8 hours when peritoneal dialysis was commenced. No recurrence of acidosis was observed during fomepizole therapy.

Hazouard et al.[183] reported the clinical course in a 46-year-old ethanol abuser who was admitted after ingesting wood alcohol in combination with ethanol. On admission he was drowsy, he complained of blurring of his vision and of photophobia. Folinic acid, 100 mg every 4 hours, was administered. The blood methanol concentration on admission was 29 mg/dL (290 mg/L) and the methanol concentration increased further with a serum ethanol concentration of 276 mg/dL (2760 mg/L). Fomepizole, 10 mg/kg, was substituted followed by a continuous infusion of 20 mg/kg/24 hours. The patient made a full recovery.

Fomepizole Dose

Human volunteer and animal studies have demonstrated that serum fomepizole concentrations in excess of 0.8 mg/L (10 μmol/L) provide constant inhibition of alcohol dehydrogenase.[172,201] In the study of humans reported by Brent et al.,[53] a 15 mg/kg intravenous loading dose of fomepizole followed by further intravenous bolus doses of 10 mg/kg every 12 hours for four doses and then 15 mg/kg 12-hourly produced serum fomepizole concentrations in excess of 0.8 mg/L.

Table 4 outlines the U.S. manufacturer's recommended dosing schedule of fomepizole during hemodialysis when the dosing interval of fomepizole should be 4-hourly. There are presently insufficient clinical data to confirm the validity of this recommendation. Alternatively, data from a case report suggest that an infusion of fomepizole 1–1.5 mg/kg/h during dialysis is sufficient to maintain therapeutic concentrations of fomepizole >0.8 mg/L.[197]

Monitoring of fomepizole concentrations for clinical reasons is unnecessary. Currently, there are no specific

Table 4

U.S. Manufacturer's Recommended Dosing Schedule of Fomepizole During Hemodialysis

Dose at the Beginning of Dialysis	
$<$ 6 hours since last dose	Do not administer dose
$\geq$ 6 hours since last dose	Give next scheduled dose
Dosing during hemodialysis	
Every 4 hours	
Dosing at the time dialysis is completed	
$<$ 1 hour since last dose	No additional dose at end of dialysis
1–3 hours since last dose	Administer 50% of next scheduled dose
$>$ 3 hours since last dose	Administer next scheduled dose
Maintenance dosing off dialysis	
Administer next scheduled dose 12 hours after last dose	

dosing recommendations for special populations such as the elderly, children, or patients with hepatic, or renal dysfunction because of the lack of clinical data.

Fomepizole Administration

In the United States, fomepizole is only available as a parenteral solution. Each vial contains 1.5 g fomepizole. The solution is a clear-to-yellow, water-soluble liquid, which may solidify at room temperature because its melting point is 25°C (77°F). If the solution has solidified in the vial, it should be warmed to liquefy it. Solidification does not affect the stability of fomepizole. Its current shelf life in the United States is 4 years.

Fomepizole should be diluted in at least 100 mL sterile 0.9% sodium chloride, or 5% dextrose solution and infused over at least 30 minutes as the undiluted formulation causes venous irritation. When refrigerated or stored at room temperature, diluted solutions of fomepizole may be used for up to 24 hours after mixing.[198]

Use of Fomepizole in the Pregnant Patient

Animal studies have not been conducted to assess the effect of fomepizole on reproduction. There are no data on the excretion of fomepizole in breast milk. Consequently, fomepizole should be administered to pregnant or breast-feeding women only after careful consideration of the risks and benefits, including the alternative of administering ethanol.

Adverse Effects of Fomepizole

During clinical trials, the most commonly reported adverse effects were as follows: headache (12%), nausea (11%), and dizziness (7%).[198,201] These adverse effects were mild and transient despite fomepizole concentrations in excess of the therapeutic concentration of 0.8 mg/L.[53] Less common adverse reactions include vomiting, diarrhea, abdominal pain, tachycardia, hypotension, vertigo, lightheadedness, nystagmus[202] slurred speech, and inebriation. Case reports have temporally associated eosinophilia,[203,204] and skin rash.[204]

In the case series reported by Brent et al.,[53] adverse events in 6 of 11 patients were classified by the treating physicians as possibly related to fomepizole. These were phlebitis, dyspepsia, anxiety, agitation, hiccups, a reaction at the infusion site, transient tachycardia, transient rash, and a "strange" feeling. Each of these events occurred in only one patient, except for agitation, which was reported by two patients. The rash occurred after four doses of fomepizole in a patient who had a history of allergic reactions to sulfonamide drugs and who was also receiving methadone, clonidine, lorazepam, and vitamins. He received two additional doses of fomepizole, with no recurrence of rash.

Adverse events were recorded in 4 of 14 patients in the case series reported by Mégarbane et al.[179] Nausea and headache occurred in one patient, lymphangitis, a burning skin sensation and mild transient eosinophilia in a second patient, and fever was observed in two patients.

Transient mild elevation of serum hepatic transaminase concentrations lasting 1–2 weeks has been observed following the administration of fomepizole.[205] However, abnormal liver function was not reported in two prospective trials involving 19 patients treated for ethylene glycol poisoning,[206] and in 25 patients poisoned with methanol treated in two case series.[53,179] On the other hand, a mild, transient elevation in one or both serum transaminase concentrations was observed in

6 of 15 volunteers administered fomepizole,[205] possibly because many received fomepizole for more than 48 hours. In studies in the rat, fomepizole did not cause hepatotoxicity at doses that block ethanol metabolism.[207,208]

At a 100 mg/kg dose of fomepizole, three volunteers developed a feeling of inebriation characterized by dizziness and mild difficulties with speech and vision.[201]

Inflammation may occur at the site of the infusion, particularly if the dose of fomepizole exceeds 25 mg/mL over 5 minutes.

There are no studies on the carcinogenic potential of fomepizole.

Fomepizole–Ethanol Interaction

Both fomepizole and ethanol alter the metabolism of each other. In four healthy male volunteers, serum ethanol concentrations of 50–150 mg/dL (500–1500 mg/L) reduced the elimination rate of a 5 mg/kg intravenous dose of fomepizole by 50%.[209] The administration of fomepizole 10–20 mg/kg followed 1 hour later by ethanol 0.5–0.7 g/kg produced a 40% reduction in the elimination of ethanol.

Folinic Acid

Therapy for methanol poisoning is focused on supportive care, including the correction of acid–base disturbances, preventing the metabolism of methanol to its toxic metabolite formic acid, and enhancing the elimination of formic acid through hemodialysis or folinic acid-enhanced metabolism. The potentially valuable use of folinic acid to enhance the metabolism of formic acid has often been overlooked. While there are no human clinical trials that confirm the benefit of using a folic acid derivative for this purpose, the animal models and the use of human liver homogenates and other human cells suggest that folinic acid administration may be beneficial.[74,210]

Rationale

In humans, formic acid is slowly metabolized to carbon dioxide and water. The morbidity and mortality associated with methanol poisoning is attributed largely to formic acid accumulation. Folate enhances formic acid metabolism, and is thereby postulated to reduce toxicity.[48] More precisely, formate is converted to 10-formyl tetrahydrofolate by the ATP-dependent activity of 10-formyl tetrahydrofolate synthetase. This is followed by the oxidation of 10-formyl tetrahydrofolate to carbon dioxide, which is catalyzed by 10-formyl tetrahydrofolate dehydrogenase.[211] It has been demonstrated that rats are less sensitive than primates to the toxicity of methanol.[72,212] Innate sensitivity, as measured by morbidity and mortality, is related indirectly to the presence of folate derivatives—the greater the efficiency of the folate pathway, the less sensitive to the toxicity of formic acid derived from methanol. These differences among rodents and primates have helped to elucidate how folate serves as a metabolic substrate or catalyst and support the use of folinic acid as an adjunct in the management of methanol-poisoned patients.

Primates have up to 60% less hepatic stores of folate than rodents. They accumulate formic acid as manifested by the development of metabolic acidosis, whereas rodents do not.[71,212] This is attributed to the presence of higher tetrahydrofolate concentrations in the liver of rodents. When laboratory rats are subjected to folate deficiency, formic acid accumulates and they also develop methanol-related toxicity.[69,178,213] The presence of endogenous folate may explain why there is no formate accumulation when methanol is inhaled during an occupational exposure under short-term conditions.[214] However, this may be a dosing effect. When a greater inhalational exposure occurs, the folate capacity of the liver would be overwhelmed, with the expectant formate accumulation and toxicity. The presence of a folate derivative is thought to enhance formate oxidation by preventing the development of enzyme catalyst deficient metabolic pathways.[71,211,212] Another proposed mechanism for the accumulation of formic acid that is independent of folate is the formate-mediated depletion of ATP which occurs through the folate-dependent pathways.[211,215]

Folinic Acid vs. Folic Acid

Folinic acid, also known as citrovorum factor, leucovorin calcium and 5-formyl tetrahydrofolate, is the reduced form of folic acid. In vivo, it is converted rapidly to tetrahydrofolic acid derivatives that are the primary bioactive and storage forms of folate in the body.[216] Although folinic acid is preferred to folic acid since it does not require metabolic reduction, folic acid is a suitable alternative if folinic acid is unavailable.

Administration and Dosage of Folinic Acid

From the perspective of the FDA, folinic acid administration to a methanol-poisoned patient is an

unapproved off-label use. However, it is a drug with a high therapeutic margin and thus, is relatively safe. Folinic acid should be considered as part of the conventional therapy of methanol poisoning. The optimal dose of folinic acid in a methanol-poisoned patient has not been established. The suggested dose is 1 mg/kg/body weight, up to a total dose of 50 mg, administered intravenously, every 4–6 hours until methanol and formate have been eliminated.[217] Folinic acid should be diluted in 5% dextrose in water and administered over 30–60 minutes.[217]

Dialysis

Hemodialysis has been used routinely to correct acidosis, to remove the toxic metabolite, formate, and to shorten the course of hospitalization by removing methanol.

Efficacy of Hemodialysis—Methanol Clearance Rates

Hemodialysis is substantially superior to peritoneal dialysis for the removal of methanol and its toxic metabolite, formate.[6,218,219] The mean clearance rate of methanol during this procedure is approximately 125–215 mL/min depending on the blood flow rate.[6,52,220,221] For example, the clearance rate of methanol was 170 mL/min when the blood flow was 270 mL/min during hemodialysis.[6]

In man, formate possesses a relatively slow, folate and pH dependent elimination rate.[25,50,61] Hemodialysis effectively removes it, and restores normal acid–base balance.[55] In one case, formate dialysance was calculated as 203 mL/min.[61] In another report including two patients treated with ethanol and folate, but in which only one received hemodialysis, the formate half-life was 3.7 hours in the patient who did not undergo dialysis and 1.1 hours in the patient who did.[147]

Indications

Hemodialysis should be considered for the following conditions: significant metabolic acidosis ($<7.25–7.30$), abnormalities of vision, deteriorating vital signs despite intensive supportive care, renal failure, or electrolyte imbalance unresponsive to conventional therapy.

In addition, a traditional indication for hemodialysis is a serum methanol concentration >50 mg/dL (>500 mg/L).[220,222] Although this concentration is often used as an indication for hemodialysis, prognosis, particularly death or permanent visual disturbance has been linked to the degree of acidosis, not the serum concentration of methanol.[2,24,52,81,143,171] Dialysis has frequently been recommended based on serum concentration alone because of the prolonged elimination of methanol and the toxic effects of therapeutic ethanol. In six patients, the serum half-life of methanol during ethanol therapy was approximately 43 hours.[34] At this rate, a methanol concentration of only 100 mg/dL (1000 mg/L) would not be reduced to the point at which ethanol or fomepizole administration could be discontinued for 3–5 days. Keeping intoxicated patients monitored on intensive care wards for that period has been considered "unbearable" for the patient and staff and is very expensive.[162]

In contrast, the use of fomepizole may obviate the need for hemodialysis, because the patient is not intoxicated and intensive care monitoring is not required.[53,162] Dosing is only twice daily. In four patients receiving fomepizole therapy, serum methanol half-life was 54 hours.[53] Hemodialysis may still be considered if rapid elimination is desired. The risks, costs, and inconvenience of prolonged hospitalization and the cost of fomepizole must be weighed against those of hemodialysis. If patients with high serum concentrations of methanol are not treated with hemodialysis, folate analogues should be administered and the patient's acid–base balance should be monitored closely with hemodialysis instituted if a metabolic acidosis develops.

Methods

The traditional endpoint for dialysis is an undetectable serum methanol concentration or a concentration below 25 mg/dL (250 mg/L) with the disappearance of acid–base imbalance. When methanol concentrations are high, dialysis of 18–21 hours may be required to reach these endpoints.[223,224] Ophthalmological abnormalities may persist transiently or permanently and should not be considered an indication for continued dialysis.[220] Redistribution of methanol may result in elevation of the methanol concentrations up to 20 mg/dL (200 mg/L) usually within 36 hours after hemodialysis ceases[6,225] and repeat hemodialysis may be necessary. In one case with an extremely high starting methanol concentration, redistribution resulted in an increase of 40 mg/dL (400 mg/L) within 6 hours.[225] Consequently, serum osmolality and serum electrolytes should be monitored every 2–4 hours for the 12–36 hour period after hemodialysis ceases.

Prolonged dialysis may not be necessary in a select group of patients receiving ethanol or fomepizole once the serum methanol concentration falls below 50 mg/dL (500 mg/L).[6] Case reports describe patients who recovered without sequelae following the termination of dialysis with the serum methanol concentration between 35–50 mg/dL (350–500 mg/L).[189,220] These patients had normal kidney function, and no significant metabolic acidosis. Additionally, they received an ethanol infusion until the methanol concentration was undetectable. Correction of the anion gap metabolic acidosis and the osmolar gap are adequate endpoints for dialysis, particularly when the patient is receiving fomepizole or ethanol and the serum methanol or formate concentrations are unavailable.

Increased administration of ethanol[189] (or the addition of 95% ethanol to the dialysate[226–228]) is necessary to counteract its loss during dialysis. Increased fomepizole dosing is also necessary during this procedure.[200] Administration of ethanol or fomepizole should continue several hours after the cessation of dialysis to provide protection from any potential rebound of the serum methanol concentration. Antidote administration can be stopped when it is determined that this value is less than 20 mg/dL (200 mg/L). Continued dialysis is not required for patients with ophthalmological abnormalities alone or symptoms related to cerebral hemorrhage, infarct, or coma. Hypophosphatemia is a rare complication of the prolonged dialysis of patients, who have normal serum phosphorus concentrations originally. Treatment to prevent this complication includes the use of phosphorus-enriched dialysate during hemodialysis.[226,227]

APPENDIX 1

Review of the Activated Charcoal Alcohol Literature

In Vivo Studies

Mathangi et al.[166] examined the use of oral activated charcoal in methanol-poisoned rats. Fasted Wistar rats (males and females, 200–250 g) received methanol in a minimum lethal dose (9.5 g/kg intraperitoneally or 14 g/kg orally). The rats were divided into control groups that received no activated charcoal and treatment groups that received activated charcoal 250 mg suspended in distilled water 1 mL three times daily. There was no indication as to whether the control group received plain distilled water 1 mL three times daily or whether the animals had access to food and water over the 48-hour observation period. Furthermore, the methodology failed to describe when the first dose of activated charcoal was administered with regard to the time of methanol administration. The eight rats that received methanol orally, but no activated charcoal, suffered 100% mortality. The seven rats in the methanol intraperitoneal administration group had a 57% survival rate without activated charcoal. In the activated charcoal treated groups, 85% of the eight rats that received intraperitoneal methanol survived, and 40% of the 25 methanol orally treated rats survived. This model suggests that activated charcoal adsorbs methanol. Although not pronounced by the authors, the study implied that methanol might undergo, to some degree, an enteroenteric secretory process that would lend itself to multiple dose charcoal administration. However, the authors encouraged further study in primates. The animal model and the limitations of the methodology preclude drawing any conclusions from this study.

In Vitro Studies

Decker and colleagues[167] investigated the adsorption of methanol by activated charcoal using an in vitro stomach model which consisted of incubating artificial gastric fluid 100 mL, methanol (1, 10, 50, or 100 mL) and activated charcoal (presumably USP, but not specified) 5 g in an Erlenmeyer 500 mL flask at 37°C. Each of the methanol samples was incubated while being shaken with a mechanical agitator for 20 minutes. The activated charcoal was separated from the liquid phase with filtration and the filtrate was analyzed to determine the percentage of methanol that was adsorbed by activated charcoal. At 1, 10, 50, and 100 mL of methanol 59, 48, 35, and 26%, respectively, were adsorbed by activated charcoal. This in vitro model demonstrated that a ratio of one part of activated charcoal to 20 parts of methanol adsorbed 26% of the methanol and the percentage adsorbed increased as the ratio of activated charcoal to methanol increased. It is not clear if this was a peer-reviewed manuscript since it appeared in a meeting supplement issue.

Other Relevant Aliphatic Alcohol Studies

Since methanol is an aliphatic alcohol, there is a proclivity toward extrapolating data from in vivo studies on ethanol directly to methanol. Olkkola[168] studied the effect of ethanol on the antidotal efficacy of activated charcoal in vitro and in experimental animals. Using an activated charcoal–strychnine model, the addition of

ethanol impaired significantly the adsorptive capacity of activated charcoal. In a similar study, Neuvonen, Olkkola and Alanen[169] investigated the effect of ethanol and pH on the adsorptive capacity of various pharmaceutical agents to activated charcoal both in vitro and in human subjects. In vitro, the addition of ethanol to activated charcoal and salicylates, quinidine, and amitriptyline impaired significantly the adsorptive capacity of activated charcoal. However, in vivo ethanol did not impair the adsorptive capacity of activated charcoal nor did activated charcoal impair the absorption of ethanol. While some of the results imply that ethanol adsorption competes preferably for binding sites, the alternative explanation is that organic solvents such as ethanol (and methanol) compete with the surface of the activated charcoal molecule and prevent adsorption of the marker substance. However, that does not imply that ethanol (or methanol) is actually adsorbed by activated charcoal. These mixed and varied results do not support or refute the use of activated charcoal in methanol poisoning.

A study by Peterson et al.[170] assessed the effect of activated charcoal on ethanol blood concentrations in dogs. Laboratory dogs (15.1–20.0 kg) were fasted for 12 hours, sedated, and given oral ethanol 2 mL/kg (control) or activated charcoal 50 g followed 30 minutes later by oral ethanol 2 mL/kg. Blood ethanol concentrations were determined at intervals for 4 hours. Activated charcoal reduced ethanol blood concentrations at 30, 60, 120, and 180 minutes by mean values of 39.2, 37.9, 27.3, and 19.1%, respectively. A significant limitation of this study is that it measured peak concentrations at a specific point in time and not the area under the absorption curve. It must be considered that this does not represent the adsorption of ethanol by activated charcoal but instead the influence of activated charcoal on reducing gastric emptying. While this study has no direct extrapolation to the use of activated charcoal in methanol poisoned patients, it is conceivable that authors may attempt to extend the conclusions to methanol.

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