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# Selected Topics Toxicology

## METHANOL POISONING

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**Abstract**—Methanol poisoning is an uncommon but an extremely hazardous intoxication. Since methanol is a versatile fuel and is having increasing usage in an energy-conscious society, a high index of suspicion and swift laboratory confirmation is essential in managing this poisoning. Methanol poisoning may occur in sporadic or epidemic circumstances. Chronic exposure may occur in the occupational setting. Man is uniquely susceptible to methanol toxicity, perhaps dependent upon folate metabolism. Classic symptoms of methanol toxicity can only occur in laboratory animals who are rendered folate deficient. Folate may be useful in humans enhancing removal of the toxic products of methanol poisoning. The enzyme responsible for metabolism of methanol is alcohol dehydrogenase. Ethanol has a higher affinity for this enzyme and is preferentially metabolized. Simultaneous ethanol and methanol administration may confuse the onset of the intoxication. Pyrazoles may also be used to inhibit alcohol dehydrogenase thus preventing the intoxication. The most important initial symptom of methanol poisoning is visual disturbance. The symptoms may be delayed up to 24 hours after ingestion due to simultaneous alcohol administration and metabolic processes. Laboratory evidence of severe metabolic acidosis with increased anion and osmolar gaps strongly suggest the clinical diagnosis. There may be an important association between mean corpuscular volume which is

significantly higher in cases of severe methanol poisoning than in mild cases. Once the diagnosis is suspected, a blood level from methanol should be returned rapidly. Treatment of methanol toxicity after good supportive care is to diminish the metabolic degradation of methanol with simultaneous ethanol and then to perform hemodialysis and alkalinization to counteract metabolic acidosis. Folate should also be administered to enhance metabolic breakdown of formate. Alcoholic patients may be especially susceptible to methanol poisoning due to relative folate deficiency.

**Keywords**—methanol; formate; 4-methyl pyrazole; anion and osmolar gaps

Methanol (methyl alcohol) can be derived from a large number of unused and discarded potential energy sources, and has excellent combustion mixing properties. For this reason it has been proposed as a gasoline additive, as a home heating material, and as feedstock in bacterial synthesis for protein. The home application of methanol includes the use of "canned heat," such as Sterno<sup>®</sup>, and the use of windshield washing materials. In addition, it is a common component of paints, varnishes, solvents, antifreeze solutions, and is utilized both in

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denaturing ethanol and as an alternative fuel source.

Methanol is generally obtained from the destructive distillation of wood; the greater the extent of distillation the more palatable the odor of the methanol. Methanol may contain impurities which impart to it a disagreeable odor and taste. Without impurities methanol more easily contributes to dangerous accidental and deliberate poisonings which can reach epidemic proportions.

The toxicology of methanol was not understood for many years. Wines, brandies, and whiskeys containing a substantial percentage of methanol were sold in the late 1800s. Results of early experiments with animals were inconsistent in describing methanol's toxicity. It was not until the late 1920s when a group of workers in Germany were poisoned with chemically pure methanol that the true toxicity of methanol was generally accepted. Bennett and his associates<sup>1</sup> reported their observations on 323 patients who ingested bootleg whiskey in Atlanta, Georgia during 5 days in October 1951. Forty-one deaths occurred when 90 gallons of the methanol-contaminated whiskey were distributed throughout the city. Later analysis of the confiscated material showed it contained 35% to 40% methanol. As word of the poisoning spread by rumor, newspaper, and radio, a minor panic developed and numerous asymptomatic individuals presented themselves to be evaluated. Kane and coworkers<sup>2</sup> reported an epidemic of poisoning in 18 individuals (of whom 8 died) when a diluted paint thinner was used as an alcoholic beverage in Lexington, Kentucky. The liquor was served as a party refreshment. Naraqui and associates<sup>3</sup> reported a severe outbreak of methanol poisoning in Port Moresby, New Guinea, in March 1977 when 28 men attended a party and consumed the contents of a drum of methanol that had been found in another village. Some of these individuals may have consumed as much as 600 mL of pure methanol. Four died, six had bilateral visual impairment, and two had persistent difficulty with speech.

Swartz and his colleagues<sup>4</sup> reported an epidemic in the State Prison of Southern Michigan in May 1979. In this instance several inmates obtained a quantity of diluent, ordinarily used in photocopying machines, which was nearly pure methanol. The inmates distributed this fluid in small quantities as "homemade" spirits. Forty-six definite cases of intoxication were identified; they were either treated initially in the prison infirmary, or referred to a local hospital center for further evaluation and treatment. Three deaths occurred; one specimen of the beverage retrieved from an inmate revealed a pink fruity liquid which was 4% methanol by weight.

Children have also become intoxicated by methanol. A 10-week-old infant was admitted to a hospital with a methanol level of 213 mg/dL nine hours after methanol was mistaken for distilled water and mixed with formula.<sup>5</sup> An 8-month-old child died when methanol-soaked pads were placed on the chest to treat a common cold.<sup>6</sup> Further emphasizing the dermal and respiratory absorption of methanol, the Polish literature reports a painter who accidentally spilled methanol on his clothes and shoes but continued to wear the soaked garments; blindness developed within several days.<sup>7</sup>

### **Methanol Toxicology**

Pure methanol is a colorless liquid, has a specific gravity of 0.81, a boiling point of 65°C, and a slight odor distinctly different from that of ethanol. Methanol can be absorbed through the skin, and through the respiratory and gastrointestinal tracts. The current threshold limit value for methanol in industry is 200 ppm (260 mg/m<sup>3</sup>). Normal methanol blood concentrations derived from endogenous production and dietary sources are approximately 1.5 mg/L. There is great variability in the mean lethal dose among animal species.

The special susceptibility of man to methanol toxicity is thought to be due not

to methanol itself, but to its metabolite, formate. Review of clinical findings in epidemic situations and in isolated cases shows great variation in the dose of methanol required to produce acidosis, blindness, and death. Some of this clinical confusion may be explained by individual metabolic differences, associated ethanol consumption, or availability of essential cofactors needed for methanol or formate metabolism. The smallest amount of methanol reported to cause death is 15 mL of 40% methanol; the highest dose recorded for a survivor is in the range of 500 to 600 mL.<sup>3</sup> Most cases of severe human poisoning occur by the oral route. Occasional cases occur by skin contact and inhalation.

Methanol is rapidly absorbed from the gastrointestinal tract, with peak absorption occurring in 30 to 60 min depending on the presence or absence of food in the stomach. Methanol distributes in total body water, although its passage through cellular membranes may be different from that of water. The primary method of elimination of methanol in humans is by its oxidation to formaldehyde, formic acid, and carbon dioxide. Methanol may also exit the body with induced vomiting, and a small amount is excreted in the breath, sweat and urine. Increasing urine flow would be expected to increase methanol excretion to some extent, but forced diuresis would not be expected to significantly increase clearance of methanol.<sup>8</sup> Several reviews<sup>9,10</sup> have described the metabolism of methanol and its metabolites in humans. It is difficult to study methanol poisoning in experimental animals because in non-primates doses of methanol that predictably cause toxic reactions in humans cause only intoxication similar to that of ethanol. Recent studies,<sup>11</sup> however, using rhesus and pig tail monkeys have been able to provide a model for human methanol intoxication. In monkeys treated with formate alone, toxic effects developed in the optic nerve similar to those observed in humans.<sup>12</sup> Formate probably inhibits cytochrome oxidase in the optic nerve, disturb-

ing the flow of the axoplasm and thus causing the pathological condition of the eye.<sup>13</sup> Current evidence does not suggest that formaldehyde causes these effects on the eye.

Due to their high rate of metabolism of formate, rats do not accumulate it; hence, rats do not manifest methanol toxicity. A folate-dependent system is likely to be responsible for the oxidation of formic acid to carbon dioxide in the liver of rats, monkeys, and probably in humans. The level of folate appears to be critical for formate metabolism in animals. The classic symptoms of methanol toxicity in rats can only be produced by rendering these animals folate deficient.<sup>14</sup> Experiments in monkeys strongly suggest that folate decreases formate accumulation after methanol overdose by stimulating formate oxidation; this suggests that folate may be useful in reducing the toxicity of methanol.<sup>14</sup>

The enzyme primarily responsible for methanol oxidation in the liver is alcohol dehydrogenase (ADH). Ethanol has a higher enzyme affinity for ADH and is preferentially metabolized; as a result, methanol is eliminated primarily by extrahepatic routes when ethanol is present. Ethanol concentrations in the range of 100 to 200 mg/dL are clinically regarded as being optimal for saturating alcohol dehydrogenase to prevent methanol metabolism. Although zero-order kinetics have been utilized to describe ethanol elimination, several investigators have shown dose-dependent characteristics of ethanol.<sup>15</sup>

Pyrazoles are also known to be potent inhibitors of alcohol dehydrogenase, but pyrazole compounds in general are too toxic for human use. One pyrazole compound, 4-methyl-pyrazole (4-MP), alone or in combination with other therapy, may be of value in methanol or ethylene glycol poisonings.<sup>16,17</sup>

Recent studies in isolated cases of methanol poisoning suggest that the associated metabolic acidosis is a result of formic acid accumulation.<sup>18</sup> The key role of formate in causing pathological damage to the eye as well as causing acidosis has only recently

been appreciated due to new assay techniques for formic acid.<sup>18</sup> Thus some of the variability in the toxicology of methanol is based upon presence of folate deficiency, simultaneous alcohol consumption, and total dose of methanol ingested.

Pathological findings of methanol poisoning have been described in detail.<sup>1,9</sup> The primary site of the ocular injury produced by methanol is in the optic nerve head and the intraorbital portion of the optic nerve, rather than in the retinal ganglia. Hemorrhages into portions of the brain are also an important aspect of methanol poisoning. Cerebral computed tomography in methanol intoxication has shown necrotic areas in the putamen.<sup>19</sup> The putamen may be a specific target for methanol toxicity. Pathological damage to the liver, pancreas and kidneys have also been described but are not specific.

### **Clinical Symptoms of Methanol Poisoning**

The appearance of clinical symptoms in methanol poisoning is affected by the amount of ethanol simultaneously ingested and by associated medical conditions. Particularly important is the time it takes symptoms to develop and the identification of abnormal laboratory test results specifically referable to methanol. In epidemic circumstances the diagnosis of methanol poisoning may be easily established; however, in isolated cases the diagnosis may be confusing. Methanol may be ingested by alcoholic patients as an alcohol substitute, and the sporadic case in a chronic alcoholic presents special problems for clinical diagnosis. It may be difficult to elicit symptoms of visual disturbances, and there may be a long delay in the onset of symptoms. Associated head trauma may provide confusing neurological findings, and early evidence of acidosis may be misinterpreted as alcoholic ketoacidosis.

The most important initial symptom of methanol poisoning is visual disturbance. Complaints of blurred vision with a relatively clear sensorium strongly suggests the diagnosis of methanol poisoning. Headache, dizziness, nausea, vomiting and abdominal pain may accompany visual disturbances. Frequently there is a complaint of breathlessness, even if acidosis is not pronounced. In severe cases an odor of formalin has been noted on the breath or in the urine. The development of bradycardia, prolonged coma, seizures, and resistant acidosis indicate a poor prognosis.

Physical findings in methanol poisoning are generally nonspecific. The acidotic, tachypnic patient may appear acutely ill. Fixed, dilated pupils have been described in severe cases. Ophthalmological examinations may be normal but may also show severe hyperemia of the optic disc and retinal edema. Optic atrophy is a late finding. On occasions, nuchal rigidity suggests meningitis. Two-thirds of patients with methanol poisoning complain of headache associated with dizziness. The most common cause of death in methanol poisoning is a peculiar, sudden cessation of respiration.<sup>1,8</sup>

### **Laboratory Diagnosis**

Laboratory evidence of metabolic acidosis with increased anion and osmolar gaps strongly suggests the clinical diagnosis of methanol poisoning. The decreased serum bicarbonate concentration is a uniform feature of severe methanol poisoning. There is often a pronounced anion gap which is not explained on the basis of diabetic acidosis, lactic acidosis, uremic acidosis, starvation, or alcoholic ketoacidosis. Ethylene glycol, paraldehyde, and salicylate are toxins that may cause an anion gap. Ethylene glycol will usually not cause visual symptoms and may be associated with oxalate crystals in the urine. Ethylene glycol may also be associated with central nervous system excitation, and increase in

muscle enzymes with hypocalcemia. The toxicology laboratory can quickly assess blood salicylate levels.

Osmolality is a reflection of the number of molecules dissolved in a liquid. In the clinical laboratory, osmolality is usually determined by measuring the freezing point of the solution. Sodium, urea, and glucose are substances that primarily contribute to normal serum osmolality. The difference between the measured osmolality and the calculated osmolality from known concentrations of major osmolar constituents in the serum is known as the osmolar gap. Using the formula shown in Figure 1, the calculated mean serum osmolality of normal persons is approximately 285 mosm/kg H<sub>2</sub>O with a standard deviation of  $\pm 4.2$  mosm/kg H<sub>2</sub>O. Theoretically, a substance will significantly contribute to the osmolality of the serum only when it exhibits a high blood level and has a low molecular weight. In an emergency room the serum osmolality determined by freezing point lowering is a rapid measure of detecting intoxication with ethanol, isopropyl alcohol, ethylene glycol and methanol. Thus, visual symptoms, acidosis, anion gap, and unexplained osmolar gap will lead to the clinical diagnosis of methanol poisoning.

Table 1 shows molecular weights, and expected osmolalities of ethanol, isopropyl alcohol, ethylene glycol, methanol and ethchlorvynol. Isopropyl alcohol may also cause depressed central nervous system function and an unexplained osmolar gap. However, it does not cause severe acidosis, and will cause acetonemia with a relatively

**Table 1. Several Toxic Substances and their Effect on Serum Osmolality at Representative High Blood Levels**

Substance	Molecular Weight	Sample Blood Level (ppm)	Expected Osmolalities (mosm/kg of water)
Ethanol	46	350	80
Isopropanol	60	350	60
Ethylene Glycol	62	200	40
Methanol	32	80	30
Ethchlorvynol	144	15	1

normal serum glucose. Occasional cases of isoniazid poisoning, carbon monoxide, lead, or arsenic intoxication may confuse the differential diagnosis in an alcoholic patient.

Swartz and his colleagues<sup>4</sup> noted an unexpected hematological findings in the epidemic of methanol poisoning at the State Prison of Southern Michigan. They found an association between red blood cell indices and the clinical severity of methanol poisoning. The mean corpuscular volume (MCV) was significantly higher in cases with moderate or severe complications of methanol poisoning. They also found that the mean corpuscular hemoglobin concentration (MCHC) was significantly lower in those methanol poisoned patients with the highest MCV. These results suggested to them that hemoconcentration alone could not explain the tendency toward a higher hematocrit and hemoglobin concentration in the more severely poisoned patients. They concluded that in severe methanol poisoning there is a primary increase in red blood cell size which correlates well with the severity of methanol poisoning. These investigators also performed in vitro experiments incubating normal red blood cells in toxic concentrations of methanol. There were no changes in red blood cell indices after 48 hours of incubation. Similar results were found in experiments using formic acid rather than methanol itself. They concluded that the red blood cell

$$2 \text{ Na} + \frac{\text{BS}}{18} + \frac{\text{BUN}}{2.6} = 285 \pm 4.2 \text{ mosm/kg H}_2\text{O}$$

**Figure 1. Formula to calculate serum osmolality. Na = serum sodium concentration mEq/L; BS = blood glucose concentration mg/dL; BUN = blood urea nitrogen concentration mg/dl.**

**Table 2. The Approximate Loading Dose and Infusion Rates of Ethanol in Treating Methanol Poisoning in a 70-kg Adult**

	Loading Dose	During Dialysis	After Dialysis
Ethanol (sp gr 0.79)	42 g	12-18 g/h	5-11 g/h
Intravenously, 10% (7.9 g/dL)	530 mL	150-230 mL/h	60-140 mL/h
Orally, 43% (86 proof, 34 g/dL)	125 mL	35-55 mL/h	15-35 mL/h

indices in vitro are not affected by simple addition of the toxins to whole blood. The mechanism responsible for their clinical findings in these methanol poisoned patients remains unexplained.

### Treatment

It is essential that a blood methanol level be determined as soon as possible if methanol poisoning is suspected. If clinical suspicion of methanol poisoning is high, treatment with ethanol should not be delayed pending the reporting of blood methanol levels. Methanol levels in excess of 50 mg/dL are probably a clinical indication for hemodialysis and ethanol treatment. With levels below 50 mg/dL ethanol treatment should be begun or continued and the test repeated.

The first treatment for methanol poisoning, as in all poisoning circumstances, is to establish respiration and create an artificial airway if necessary. Emesis can be induced if the patient is neither comatose nor seizing and has not lost the gag reflex. If these contraindications exist, the patient should be endotracheally intubated and gastric lavage carried out with a large bore tube.

In addition to attempts to limit absorption, there are three major modalities of treatment for severe methanol poisoning:

- diminishing the metabolic degradation to toxic products
- dialysis to enhance removal of methanol and its toxic products and to improve acid-base balance
- alkalinization to counteract the metabolic acidosis

Because ethanol competes for alcohol dehydrogenase, the enzyme responsible for metabolizing methanol to formic acid, it is essential to block ADH by administering the less toxic ethanol. Ethanol has a higher affinity for, and is preferentially metabolized by, alcohol dehydrogenase. The dose dependent characteristic of ethanol metabolism which occurs at increased levels, and its variability induced by chronic ethanol intake require the frequent monitoring of blood ethanol levels to ensure appropriate alcohol concentrations.

With the initiation of dialysis, ethanol will also be eliminated in the dialysate; this requires further alterations in the dose of ethanol. Table 2 lists the approximate loading dose and infusion rates during and after dialysis in a 70-kg adult. Ethanol distributes in body water, so that a loading dose of 42 g will achieve a blood concentration of approximately 100 mg/dL in a 70-kg patient. During dialysis approximately 12 to 18 g/h should be given, and after dialysis between 5 to 11 g/h. If the patient is awake or a nasogastric tube is in place, then the oral route can be utilized for ethanol by using a 43% (86 proof) alcohol. Ethanol may also be given intravenously although high concentrations of ethanol may damage veins and be painful for the patient. A 10% intravenous solution is usually optimal. The estimates of ethanol levels given here should be verified by frequent ethanol determinations, especially during dialysis. It is desirable to maintain the ethanol infusion until methanol levels are undetectable.

Since folate dependent systems are likely responsible for the oxidation of formic acid to carbon dioxide in humans, it is probably useful to administer folic

**Table 3. Indications for Ethanol Therapy and/or Dialysis after Suspected Methanol Ingestion****Indications for Ethanol Therapy**

1. History of methanol ingestion, if level not immediately available.
2. Peak methanol level greater than 20 mg/dL in an asymptomatic patient.
3. Metabolic acidosis unexplained with increased anion and osmolar gaps.

**Indications for Ethanol Therapy and Hemodialysis:**

1. Methanol levels greater than 50 mg/dL, even in an asymptomatic patient.
2. Methanol poisoning with severe acidosis *not* correctable with sodium bicarbonate.
3. Visual symptoms and suspected methanol poisoning when confirming laboratory studies not available.

acid to patients poisoned with methanol, although this has never been tested in human clinical studies. Since the effective dose of folic acid has not been tested one should probably administer at least 50 mg folic acid intravenously every four hours. This large dose is nontoxic. Also, 4-methylpyrazole (4-MP) may be a useful adjunct to methanol poisoning if it becomes available for human use.

Table 3 lists indications for ethanol therapy and dialysis in suspected methanol poisonings. With confirmation of the diagnosis of methanol poisoning and identification of a high blood level (greater than 50 mg/dL), hemodialysis is indicated.<sup>20,21</sup> Peritoneal dialysis has been shown to be less efficacious than hemodialysis.<sup>22</sup> Sorbent-based regeneration hemodialysis systems have become readily available for routine use in patients with acute and chronic renal failure. However, the sorbent-based hemodialysis systems have been shown to be ineffective in the treatment of methanol poisoning.<sup>23</sup>

Because of the profound metabolic aci-

dosis in methanol poisoning, treatment with bicarbonate therapy may also be necessary. The quantity of bicarbonate to be administered should be adjusted according to estimates of sodium intake, concern for potassium balance, and careful monitoring of cardiovascular status. A special problem occurs in patients with a relatively low methanol level who have visual symptoms. In this situation the laboratory test for methanol should be repeated and confirmed with osmolality estimates. If visual impairment is present hemodialysis should be begun independent of the methanol level.

In a recent epidemic of methanol poisoning, Swartz and his colleagues<sup>4</sup> felt that once initial acidosis had been corrected with bicarbonate, neither sustained alkali nor dialysis was required if ethanol treatment was maintained. These observations have yet to be repeated by others.

Alcoholic patients are likely to be folate deficient, and thus are more susceptible to methanol toxicity. Even if the relative increase in MCV in methanol poisoning is not the result of folic acid deficiency, therapy with folate cannot be expected to be toxic and therefore would hardly be dangerous to administer in this setting. Although conservative treatment may suffice in moderately severe methanol poisoning, hemodialysis procedures are still considered the preferred treatment in severe cases.

Methanol poisonings, whether they occur epidemically or sporadically, are uncommon but extremely hazardous poisonings. It is likely that methanol, which is a versatile fuel, will have increasing usage in an energy conscious society. It will be important that methanol-containing products have appropriate labeling and packaging that will discourage accidental intoxication. A high index of suspicion and quick laboratory confirmation are essential factors in managing methanol poisoning.

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