Methanol Ingestion

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In Brief

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Author Disclosure

Drs Fein and Sue have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Alcohols are hydrocarbons with one or more hydroxyl groups. Although all alcohols are toxic to varying degrees, the toxic alcohols refer to all but ethanol, which is consumed widely in beverages and medicinal preparations. Methanol is a single carbon alcohol that is highly toxic in very small quantities—as little as a sip in small children. Although its use in the embalming process dates back to ancient Egypt, pure methanol was not isolated until the mid seventeenth century by the chemist Robert Boyle through distilling boxwood. In fact, the word methanol derives from the Greek words for wood and wine. Today, methanol is found in many common household products such as windshield washer fluid, perfumes, portable cooking fuels, and printing solutions. In addition, methanol is used as fuel in auto racing, as an ingredient in industrial solvents, and as a denaturant in nonfood grade ethanol. Although methanol intoxication may result from vapor inhalation and transdermal absorption, most cases of methanol toxicity in the United States occur from ingestion of windshield wiper fluid.

Methanol, readily absorbed from the gastrointestinal tract and predominantly metabolized in the liver, is converted by the enzyme alcohol dehydrogenase to formaldehyde, which is further metabolized by aldehyde dehydrogenase to formic acid, the primary toxic metabolite of methanol. Both of these enzymatic reactions employ the reduction of nicotinamide adenine dinucleotide (NAD^+) to NADH as cofactors. Ultimately, in a folate-dependent rate-limiting reaction, formic acid is broken down to carbon dioxide and water. Elimination half-lives for methanol are reported variably as 15 to 30 hours.

The toxicity of methanol results primarily from its metabolites. Formic acid is itself an organic acid that produces a profound anion gap metabolic acidosis. In addition, formic acid inhibits mitochondrial cytochrome oxidase c, inhibiting oxidative phosphorylation. This arrest of aerobic metabolism contributes to the accumulation of NADH, driving the anaerobic conversion of pyruvate to lactate, thereby further exacerbating the metabolic acidosis.

In addition to its metabolic effects, methanol produces central nervous system and ocular toxicity. The initial central nervous system symptoms of methanol intoxication last only several hours and are similar to those of ethanol intoxication, although to a lesser degree: inebriation, disinhibition, and drowsiness. More ominous central effects, such as seizures, coma, and cerebral edema, are delayed by 12 to 24 hours and result from the accumulation of formic acid and ensuing severe metabolic derangements. The basal ganglia are especially vulnerable to the toxic effects of methanol. Parkinsonian-like sequelae have been reported, including dementia, tremor, rigidity, and bradykinesia. Computed tomography scan of the brain may reveal cerebral edema or bilateral necrosis of the putamen.

The optic nerve and pigmented cells of the retina are especially vulnerable to direct toxic effects of formic acid, and visual symptoms are the hallmark of methanol ingestion. Complaints include color changes, blurred vision, the characteristic "snowfield vision," and complete blindness. Physical examination reveals hyperemia or pallor of the optic discs, loss of pupillary response and, in severe cases, optic atrophy and permanent loss of vision.

In addition, massive ingestions of methanol may result in pulmonary edema, dysrhythmias, and circulatory collapse. Pancreatitis and acute renal failure are rare but have been reported. Concomitant ethanol intoxication competitively inhibits metabolism of methanol by alcohol dehydrogenase and further delays the manifestations of its toxic metabolites.

Table. Indirect Laboratory Markers of Methanol Poisoning

	Calculation	Normal Range
Anion Gap	$Na^+ - [Cl^- + HCO_3^-]$	12±4 mEq/L
Osmol Gap	Measured serum osmolality − $[2Na^+ + glucose/18 + BUN/2.8]$	−2±6 mOsm

BUN=blood urea nitrogen; Cl=chloride; HCO_3=bicarbonate; Na=sodium.

A methanol concentration of 25 mg/dL is accepted conventionally as requiring action, although this value is not well based on supporting evidence. The lack of rapidly available methanol levels in most medical centers decreases their diagnostic utility. Two indirect laboratory markers that may be useful in the evaluation of methanol toxicity are the anion gap and the osmol gap (Table). Methanol is an osmotically active compound that manifests as an elevated osmol gap shortly following ingestion. However, an elevated osmol gap is neither sensitive nor specific for methanol ingestion.

As methanol is metabolized to formic acid, the osmol gap falls, while an anion gap metabolic acidosis develops. Because of the reciprocal relationship between the osmol and anion gaps, absence of an elevated anion gap does not exclude methanol toxicity early in the course of poisoning. Ethanol levels, by inhibiting the toxic conversion of methanol, serve to explain a delay in clinical toxicity. In addition, ethanol contributes to the overall osmol gap. Arterial blood gas determination, serum electrolytes, and lactate level are also useful in the assessment and management of methanol poisoning.

The initial management of methanol poisoning should focus on support of cardio-respiratory function and decontamination. Gastric evacuation via nasogastric tube may be attempted early in the course of massive ingestions. The poor adsorption of alcohols to activated charcoal precludes the utility of the sorbent for decontamination in methanol ingestion. However, activated charcoal should be considered, given the common occurrence of coingested substances.

Secondary efforts are aimed at minimizing the toxic conversion of methanol to formic acid. Traditionally, ethanol, with its comparatively greater avidity for alcohol dehydrogenase, was administered either intravenously or orally for this purpose. Given the inherent adverse effects of ethanol (inebriation, respiratory depression, metabolic disturbances, and fluid overload) and the difficulty in maintaining stable serum concentrations, its use has been all but abandoned in favor of a safe and effective alternative, fomepizole (4-methylpyrazole). Fomepizole is an intravenously administered competitive antagonist of alcohol dehydrogenase which, unlike ethanol, is essentially devoid of adverse effects and does not require monitoring of serum concentrations. Its primary disadvantage is that it is very expensive.

Deprived of its primary route of biotransformation, unmetabolized methanol has a half-life of about 54 hours and is eliminated minimally via the kidneys and lungs. Hemodialysis is a useful adjunct to alcohol dehydrogenase blockade because it not only clears the parent compound and its metabolites but also corrects acidosis and fluid overload. Patients who develop end-organ toxicity, renal failure, or severe metabolic acidosis, or who have a serum methanol concentration greater than 50 mg/dL, should be hemodialysed. Folic acid, a necessary cofactor for the final conversion of formic acid to carbon dioxide and water, should be administered. Careful monitoring of acid-base status and fluid balance along with meticulous respiratory support help optimize outcomes.

Methanol intoxication has a high morbidity and mortality. Poor prognostic factors include severe acidosis, coma, or seizures at presentation, acute renal failure, and hypotension. Approximately one third of patients suffer long-term visual or neurologic sequelae. Maintaining a high degree of suspicion for methanol intoxication, especially in the face of an elevated osmol gap or an anion gap metabolic acidosis, is of the utmost importance because rapid identification and early intervention offer the best hope for a favorable outcome.

Comment: Methanol ingestion is only one cause of a high anion gap metabolic acidosis, and thankfully not one of the more common ones. By far, dehydration with a resulting lactic acidemia is what pediatricians see most often in association with a high anion gap. A widely used mnemonic for remembering the causes of high anion gap metabolic acidosis is MUDPILES:

> **M**ethanol, **U**remia, **D**iabetic ketoacidosis, **P**ropylene glycol, **I**nborn errors of metabolism/**I**ron/, **I**soniazid, **L**actic acidosis, **E**thanol/**E**thylene glycol, **S**alicylates.

The mnemonic has evolved over the years, with the passing of agents such as paraldehyde and phenformin, the original Ps. If you have a sweeter tooth, forget the liberty taken with spelling and remember KARMEL:

> **K**etoacidosis, **A**spirin, **R**enal failure, **M**ethanol, **E**thanol/Ethylene glycol, **L**actic acidosis.

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Editor, In Brief

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