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Acute Methanol Poisoning

'The Blind Drunk'

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In this Medical Grand Rounds, Dr. Charles Becker will present an unusual case of methanol poisoning and discuss its pathophysiology and management.*

Case Presentation

DR. BECKER:† The patient, a pathology resident, was in excellent health until two o'clock one afternoon. While doing an autopsy she noted a peculiar whiteness to her vision, "like stepping out into a snow field." There was no associated diplopia or blurred vision. The only associated symptom was mild restlessness and shortness of breath, even with minimal exertion. She had taken two aspirin tablets in the morning for a mild headache. These symptoms continued and became severe over the next four to five hours when she sought assistance in the emergency room. She had not eaten or drunk anything unusual in the preceding 24 hours. The previous evening she had eaten a home-cooked meal. With that evening meal, approximately 12 hours before the onset of symptoms, she had consumed 30 to 60 ml of 86-proof vodka that was kept in the refrigerator and had been used on several earlier occasions; she also drank two glasses of wine. Her past medical history was normal except for mild labile hypertension and pyelonephritis.

In the emergency room she appeared healthy. She was afebrile, blood pressure was 170/105 mm of mercury, pulse 110 per minute and regular, and respirations 30 per minute. Findings on physical examination were entirely normal, including results of a detailed eye examination.

Routine laboratory studies gave the following values: serum sodium 135 mEq, potassium 4.7 mEq, chloride 107 mEq and bicarbonate 6 mEq per liter. Serum osmolality was 325 mOsm per kg of water, pH 7.21, carbon dioxide pressure (P_{CO_2}) 11 mm of mercury and oxygen pressure (P_{O_2}) 123 mm of mercury. Blood urea nitrogen (BUN) was 12 mg and creatinine 1.0 mg per dl. Leukocyte count was 7,000 per cu mm. Hemoglobin and hematocrit were within normal limits. Analysis of urine showed a pH of 5.5 with no crystals evident. Electrocardiogram showed only a sinus tachycardia. An x-ray film of the chest was normal. Blood methanol level was 140 mg per dl at 7 PM and 110 mg per dl at 9 PM. A blood salicylate level was undetectable.

Oral and intravenous administration of ethanol was begun and the patient was given sodium bicarbonate each hour. Hemodialysis was started and continued for six hours. At the end of dialysis

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no methanol was detected in her blood. The patient's visual symptoms decreased dramatically during dialysis. Extensive ophthalmological investigations indicated only slight pallor of the optic disc. Evoked visual responses eight hours following dialysis were normal. The patient fortunately has had an uneventful recovery. Police investigators on the night of admission secured the vodka bottle from her refrigerator; analysis showed a 20 percent methanol content.

Methanol Toxicology

Methanol (methyl alcohol or wood alcohol) is obtained from the destructive distillation of wood. This distillation is accompanied by a distasteful smell that limits the palatability of methanol. With further distillation, the pure methanol is much more palatable and has many industrial and practical uses. Methanol is found in varnishes, shellacs, duplicating fluids, stains, enamels, plastics, films, textiles, linoleum, dyes, explosives, rubber and felt hats. Because methanol can be derived from a large number of unused or discarded sources and has excellent combustion and mixing properties, it has been proposed as a gasoline additive, as home-heating material and as a feedstock for bacterial synthesis of feed protein. Most of us recognize methanol in the form of canned heat, such as Sterno, or in windshield-washing material.

Crude wood alcohol contains many impurities, which give it a disagreeable odor and taste. When the odor is removed, methanol becomes palatable and yields an increase in accidental and deliberate poisoning, which can reach epidemic proportions.

The toxicology of methanol was not initially appreciated. Some wines, brandies and whiskeys were sold in New York City during the late 1800's that contained substantial percentages of methanol. Initially, apparent poisonings were attributed to contaminants such as acetaldehydes, allyl alcohols, acetone or fusel oils. Results of early experiments with animals were inconsistent in describing methanol's toxicity. It was not until the 1920's, when a group of dock workers in Hamburg, Germany, were poisoned with chemically pure methanol, that the toxicity of wood alcohol was generally accepted. In the classic paper in the field Bennett and associates[1] reported their observations of 323 patients who had ingested bootleg whiskey in Atlanta during five days in October 1951. Forty-one deaths occurred when 90 gallons of illicit whiskey were distributed throughout the city. Later analysis of the confiscated material showed 35 percent to 40 percent methanol and less than 4 percent ethanol. As word of the poisoning spread, by rumor, newspaper and radio, a minor panic developed and numerous asymptomatic persons presented themselves to be checked for evidence of poisoning. In many instances these persons had drunk no alcoholic beverage at all and were simply frightened.

Kane and co-workers[2] reported an epidemic of poisoning in 18 persons, of whom eight died, when a diluted paint thinner was used as a source of alcoholic beverage in Lexington, Kentucky. The liquor was served as the major refreshment at a party. Naraqi and associates[3] reported a severe outbreak of methanol poisoning in Port Moresby, New Guinea, in March 1977 when 28 men attended a drinking party in which they consumed the contents of a drum that was found near their village. Some persons may have consumed as much as 600 ml of pure methanol in this epidemic. Four died, six had bilateral visual impairment and two had persistent difficulty with speech.[3]

Children have also been affected by methanol. A 10-week-old infant was admitted to hospital after methanol was mistaken for distilled water and mixed with her formula.[4] An 8-month-old child died in Brussels when methanol-soaked pads were placed on the child's chest to treat a common cold. This custom, known to the family as "take off the cold," was done by applying warm alcohol-soaked compresses to the child's chest, which had been previously rubbed with olive oil. Having no alcohol, the mother had accidentally purchased methanol-soaked pads.[5] The Polish literature[6] also contains the history of a painter who accidentally poured methanol on his clothes and shoes and did not change them; blindness developed within several days.

Pure methanol is a colorless liquid, having a specific gravity of 0.81, a boiling point of 65°C and a slight odor distinctly different from that of ethyl alcohol. Methanol can be absorbed through the skin, respiratory tract or gastrointestinal tract. Permissible exposure limits in industry, based on an eight-hour time-weighted average, have been estimated to be in the range of 200 ppm.

There is great variability in mean lethal dose among animal species. The special susceptibility of man to methanol toxicity is probably due to a metabolite of methanol (formate) and not to methanol itself. Reviewing clinical findings in epidemic situations or in isolated cases shows an enormous variation in the dose of methanol re-

quired to produce acidosis, blindness or 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 percent methanol; the highest dose recorded for a survivor is in the range of 500 to 600 ml.[3] Most cases of severe human poisoning occur by the oral route; occasional cases occur with skin contact and inhalation. Since methanol has a low boiling point and is completely absorbed from the mucous membranes of the upper respiratory passage, there is concern about methanol being applied to the inside of a windshield of a car in cold weather or about having repeated occupational exposures.

Methanol is rapidly absorbed from the gastrointestinal tract with peak absorption in 30 to 60 minutes. It distributes itself in total body water, although passage through all cellular membranes may be different from that of water, suggesting that some cells are less permeable. Bennett and co-workers[1] noted a higher concentration of methanol in cerebrospinal fluid than in blood in patients while the blood concentrations were declining. There is little evidence to suggest that methanol is actively concentrated in the central nervous system or in the cerebrospinal fluid.[7]

The primary route of elimination of methanol in humans is by oxidation to formaldehyde, formic acid and carbon dioxide. Methanol may also exit the body by induced vomiting, and a small amount is excreted in 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.[7]

Several reviews[8,9] have described the metabolism of methanol and its metabolites in man. The difficulty in studying methanol toxicity in animals is that in nonprimates, doses of methanol that cause toxic reactions in man produce only intoxication similar to that seen with ethanol. Recent studies[10] using rhesus and pigtail monkeys have been able to provide a model for human methanol intoxication. In monkeys treated with formate alone, toxic effects develop in the optic nerve similar to those observed in humans.[11] Formate probably inhibits cytochrome oxidase in the fundi, disrupting the flow of the axoplasm and thus causing the pathological conditions in eyes.[11] Current evidence does not suggest that it is formaldehyde that causes these effects in the eyes. Rats do not accumulate formic acid because of their high rate of metabolism of formate; hence rats do not have the manifestations of methyl alcohol toxicity found in monkeys and humans.[11] A folate-dependent system is responsible for the oxidation of formic acid to carbon dioxide in the liver of 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 be produced by rendering these animals folate deficient.[12] Experiments in monkeys strongly suggest that folate decreases formate accumulation after methanol overdose by stimulating formate oxidation, thus suggesting that folate may be useful in removing methanol.[13]

The enzyme primarily responsible for methanol oxidation is liver alcohol dehydrogenase (ADH). This enzyme has pronounced species variability. Ethanol has a higher enzyme affinity for alcohol dehydrogenase and is preferentially metabolized, whereas methanol is eliminated by nonmetabolic routes when ethanol is present. Ethanol concentrations of 100 to 200 mg per dl are clinically regarded as being optimal for saturating alcohol dehydrogenase to prevent methanol metabolism.[14] Although zero-order kinetics have been utilized to describe ethanol elimination, several investigators have shown a dose-dependent characteristic of ethanol.[14] Pyrazoles are known to be potent inhibitors of alcohol dehydrogenase. Pyrazole compounds in general are toxic to humans, but one particular pyrazole, 4-methylpyrazole (4MP), alone or in combination with ethanol may be of therapeutic value in methanol or ethylene glycol poisoning.[8,14-16]

Recent studies in isolated cases of methanol poisoning suggest that the associated metabolic acidosis is a result of formic acid accumulation.[17] The key role of formate causing the pathological damage to the eye and the acidosis has only recently been appreciated due to new techniques for the assay of formic acid. Thus, some of the variability in the toxicology of methanol is based upon susceptibility to folate deficiency, simultaneous alcohol consumption and total dose of the toxin ingested. Formaldehyde is highly reactive and its intracellular distribution in tissues has made it difficult to assess the role of this toxin in the pathology of methanol poisoning, but current evidence does not suggest that this is the primary pathological metabolite of methanol.

Pathological findings of methanol poisoning

have been described in detail.[1,8] 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 the retinal ganglia. Hemorrhage into critical portions of the brain is an important aspect of methanol poisoning. Cerebral computed tomography in methanol intoxication has shown necrotic areas of the putamen.[18] Pathological damage to liver, pancreas and kidney has also been described but is nonspecific.

Clinical Symptoms and Laboratory Findings

The time it takes for symptoms to develop and the identification of abnormal laboratory test results specifically referable to methanol poisoning depend on the amount of simultaneous ethanol ingestion and associated medical conditions. In epidemic circumstances the diagnosis may be easily recognized. However, in isolated cases, such as in our patient, the diagnosis may be confusing. Some idea as to the confusion that may arise in the clinical recognition of this disorder is illustrated by the following list of initial emergency room diagnoses in patients subsequently proved to have methanol poisoning: cholera, botulism, diabetic ketoacidosis, hangover, pancreatitis, renal stone, perforated peptic ulcer, intestinal obstruction, meningitis, brain tumor and subarachnoid hemorrhage.[1] Methanol may be ingested by alcoholic patients as an alcohol substitute. 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 after ingestion. Associated head trauma may provide confusing neurological findings and early evidence of acidosis may be misinterpreted as alcoholic ketoacidosis.

The most important initial symptom, as graphically described by our patient, is indistinct vision frequently described as "like being in a snow storm." Visual disturbances are a universal complaint in the epidemic circumstance.[1] Complaints of blurred vision with a relatively clear sensorium should strongly suggest the diagnosis. Headache, dizziness, nausea, vomiting and abdominal pain may also be part of the associated symptoms with visual disturbances. Not infrequently, just as with our patient, there is a complaint of breathlessness, but Kussmaul-type respiration is not a prominent feature, even with pronounced acidosis. In severe cases, some persons have noted an odor of formalin on the breath or in urine. The development

$$Na + \frac{BS}{-} + \frac{BUN}{26} = 285 \pm 4.2 \text{ mOsm/kg } H_2O$$

Figure 1.—Formula to calculate serum osmolality. (Na = serum sodium concentration mEq/liter/dl; BS = blood glucose concentration mg/dl; BUN = blood urea nitrogen concentration mg/dl.)

TABLE 1.—*Several Toxic Substances and Their Effect on Serum Osmolality at Their Lethal Blood Levels*

	Molecular Weight	*Estimated Lethal Levels (mg per dl)*	*Expected Osmalities (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

of bradycardia, prolonged coma, seizures and resistant acidosis indicate a poor prognosis.

Physical findings are generally nonspecific. Fixed, dilated pupils have been described in severe cases. Results of ophthalmologic examinations may be normal, as in this case, but also may show severe hyperemia of the optic disc or retinal edema. Optic atrophy will be a late finding. On occasion, nuchal rigidity and signs suggesting meningitis may occur. Two thirds of patients may complain of headache associated with dizziness. The mode of death for most patients with methanol poisoning is a peculiar sudden cessation of respiration.[1,7]

Laboratory evidence of metabolic acidosis with an elevated anion gap and an osmolar gap strongly suggest the clinical diagnosis of methanol poisoning. A decreased serum bicarbonate concentration is a uniform feature of severe methanol poisoning. Just as in our patient today, there is 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 also specific 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, an increase in muscle enzymes and hypocalcemia. A toxicology laboratory can quickly give information as to a blood salicylate level. Of note in this patient was a history of two salicylate tablets taken in the morning for headache.

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 a solution. Sodium, urea and glucose are the substances that primarily contribute to this serum osmolality. The difference between the measured osmolality and the osmolality calculated from known concentrations of major osmolar constituents of the serum is known as the osmolar gap. Using the formula shown on Figure 1, the mean serum osmolality of normal persons is 286 mOsm per kg of H_2O with an SD ± 4.2 mOsm per of kg of H_2O. Theoretical considerations indicate that a substance will significantly contribute to the osmolality of the serum only if it achieves a high blood level and has a relatively low molecular weight. In an emergency room, the serum osmolality provides a rapid, convenient measure of detecting intoxication with ethanol, isopropyl alcohol, ethylene glycol and methanol.

Table 1 shows the molecular weight, estimated lethal levels and the expected osmolalities. Thus, visual symptoms, acidosis, anion gap and unexplained osmolar forces will lead to the clinical diagnosis of methanol poisoning. Isopropyl alcohol may also cause depressed central nervous system function and unexplained osmolar gap but usually does not cause severe acidosis and will cause acetonemia with a relatively low serum glucose level. Occasional cases of isoniazid poisoning, or carbon monoxide, lead or arsenic intoxication may confuse the differential diagnosis in an alcoholic patient.

It is critical that a blood methanol level be determined as soon as possible if the diagnosis is suspected. If the clinical suspicion of methanol poisoning is high, treatment should not be delayed pending the reporting of a blood level. Methanol levels in excess of 50 mg per dl are probably an absolute indication for hemodialysis and ethanol treatment. When levels are below 50 mg per dl, ethanol treatment should be begun (or continued) and the tests repeated.

The first treatment for methanol poisoning, as in all critical poisoning situations, is to establish respiration and create an artificial airway if necessary. Emesis can be induced if the patient is not comatose, is not having seizures and has not lost the gag reflex. If these contraindications exist, then the patient should be endotracheally intubated and a gastric lavage carried out with a large bore tube. There are three major modalities of treatment for severe methanol poisoning: (1) diminishment of metabolic degradation to toxic products, (2) dialysis to enhance removal of methanol and its toxic products and to improve acid/base balance and (3) alkalinization to counteract the metabolic acidosis.

Because ethanol competes for alcohol dehydrogenase, which is responsible for metabolizing methanol to formic acid, it is essential to block this enzyme by administering the less toxic ethanol. Ethanol has a higher enzyme affinity and is preferentially metabolized by alcohol dehydrogenase. Blood ethanol concentrations greater than 100 mg per dl are probably optimal for blocking this enzyme system. The dose-dependent characteristics of ethanol metabolism and the variability induced by chronic ethanol intake require the frequent monitoring of blood ethanol levels to ensure appropriate alcohol concentrations.

With the initiation of dialysis procedures, ethanol will also be eliminated in the dialysate, requiring alterations of 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 grams will achieve a blood concentration of 100 mg per dl in a 70-kg patient. During dialysis, approximately 12 to 18 grams per hour should be given and after the dialysis, between 5 and 11 grams per hour. If the patient is awake or a nasogastric tube is placed, then the oral route can be utilized for ethanol by using 43 percent (86 proof) alcohol.

Alcohol may also be given intravenously, although high concentrations of alcohol are painful. A 10 percent intravenous solution is usually required. The estimates of ethanol levels given here should be verified by frequent alcohol determinations, especially during dialysis. It is generally desirable to maintain the ethanol infusion until

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 grams	12-18 grams/hour	5-11 grams/hour
Intravenous, 10% (7.9 grams/dl)	530 ml	150-230 ml/hour	60-140 ml/hour
Orally, 86 proof (43%) (34 grams/dl)	125 ml	35-55 ml/hour	15-35 ml/hour

methanol levels are undetectable. It is also useful to remember that 1 ml of absolute alcohol contains 790 mg of ethanol (specific gravity 0.79). A 10 percent ethanol solution has 79 grams per dl and an 86-proof alcoholic beverage has 34 grams per dl.

Since folate-dependent systems are probably responsible for the oxidation of formic acid to carbon dioxide in humans, it is probably useful to administer folic acid to patients poisoned with methanol, although this has never been tested in clinical studies. 4-Methylpyrazole may also be a useful adjunct in methanol poisoning if it becomes available for human use.

With confirmation of the diagnosis of methanol poisoning and identification of a blood level higher than 50 mg per dl, hemodialysis is indicated.[19,20] Peritoneal dialysis has been shown to be less efficacious than hemodialysis.[21] In the past few years, sorbent-based regeneration hemodialysis systems (REDY) have become available as a method for routine use in patients with chronic and acute renal failure. Because the system is readily portable, is relatively small in size and has a small dialysate volume, this system can be easily tailored to an individual patient. However, the sorbent-based hemodialysis systems have been shown to be ineffective in the treatment of methanol poisoning.[22]

Because of the profound metabolic acidosis in methanol poisoning, treatment with bicarbonate therapy may be necessary. It is very unlikely that the acidosis itself causes damages or alters the outcome of the visual disturbances. Quantities of bicarbonate to be administered should be adjusted based upon estimated sodium intake, concern for potassium balance and careful monitoring of cardiovascular status.

A special problem would result if the patient had a relatively low methanol level but visual symptoms. In this situation the laboratory test for methanol itself should be repeated and confirmed with osmolality estimates. If visual impairment is present, hemodialysis should be begun independent of the methanol level.

Discussion of Case

Our patient today represents a sporadic case of severe methanol intoxication. Of note was her occupation as a pathology resident and the onset of visual symptoms while carrying out an autopsy. One of the early questions in this case involved the possibility of formaldehyde or formalin intoxication. This would seem unlikely in this case because formaldehyde and formalin are so injurious to mucous membranes, and there were no such symptoms. Methanol inhalation in the pathology laboratory also seemed unlikely in that exposure during the relatively brief time of the autopsy would not account for a blood level of methanol of 140 mg per dl. However, permissible exposure levels of methanol of 200 ppm may be exceeded by persons working with methanol and does represent a potentially serious occupational hazard. Health hazards of chronic formaldehyde exposure remain to be determined.

The initial presentation with eye symptoms in our patient is classic. The history was confused by the ingestion of two aspirin early in the morning for a headache and the 12-hour delay in the onset of her symptoms. This delay may be explained in part by her simultaneous ingestion of ethanol with her evening meal. The laboratory findings in this case illustrate an anion gap and an osmolar gap. Toxicology laboratory levels were reported and institution of ethanol administration and hemodialysis was prompt. Of special note are the normal funduscopic evaluations. The unusual method of administration of the methanol in this case is under police investigation.

Conclusion

Methanol intoxication in sporadic fashion is an uncommon but extremely hazardous poisoning. It is likely that methanol will be a versatile fuel with increasing usage in our energy-conscious society. Proposed uses of methanol should be weighed against potential hazards. Methanol is likely to become a competitor with petroleum products because it is economically attractive to derive methanol from otherwise unused or discarded sources. Since the toxicity of methanol is serious and its mortality unacceptable, every effort should be made to monitor and protect workers exposed to methanol and common sources of methanol such as windshield de-icer sprays and canned heat. These products should have appropriate labeling, and packaging should be designed to protect children. Our desire to find safer fuel sources should be tempered with the recognition of the hazard so that delivery systems of the material are protected, perhaps by adding an emetic to methanol or making sure that antisiphoning methods are employed. The blind drunk is, fortunately, an uncommon event. As in the case discussed today, methanol intoxication requires immediate diag-

nosis, institution of treatment before laboratory confirmation and a thorough appreciation of pharmacotoxicology.

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Suppression of Immunity by Cytotoxic Agents?

WHAT ABOUT cytotoxic agents? Swanson and Schwartz, years ago at Tufts New England Medical Center, showed that if you take azathioprine and mercaptopurine and give those drugs to a normal person you will significantly suppress delayed hypersensitivity and cell-mediated immunity. And these are drugs that we use in patients with Hodgkin's disease—and they already have a defect from their underlying disease. Could corticosteroids or cytotoxic agents themselves predispose to infection? After all, we have patients—say with severe asthma—receiving high doses of corticosteroids for many years, or relatively high doses. Do they get infected? The answer is not much more than the general population.

—JACK S. REMINGTON, MD, *Palo Alto, California*

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