Methanol intoxication: clinical features and differential diagnosis

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■ Methanol intoxication causes severe metabolic acidosis and can lead to permanent visual damage or death. Methanol, readily available in common products like antifreeze, is ingested accidentally or deliberately as a substitute for ethanol and in suicide attempts. Because it may become a major fuel source in the 21st century and because industrial uses are expanding, deliberate and accidental intoxication is likely to increase. Rapid diagnosis is essential so that appropriate treatment can be instituted quickly. The authors review the pharmacology, clinical and laboratory findings, and pathology and pathophysiology of methanol intoxication. In addition, they discuss the differential diagnosis and treatment of acute intoxication, including the use of 4-methylpyrazole in preventing the conversion of methanol to formate.

INDEX TERMS: POISONING, METHYL ALCOHOL CLEVE CLIN J MED 1990; 57:464–471

METHANOL (wood spirit, wood alcohol, Columbian spirit) ingestion causes a severe metabolic acidosis and visual disturbances that may become permanent despite aggressive therapy. In the past, the use of methanol in bootleg whiskey resulted in epidemic poisonings, and methanol continues to be ingested as a cheap substitute for ethanol. Methanol is also ingested in suicide attempts. It is readily obtained, and toxic amounts are present in a variety of compounds found in the home and workplace, including windshield washer fluid, antifreeze, carburetor fluid, duplicating fluid, paint remover, various solvents and cleaners, Sterno, and gasoline mixtures. If there is a move to methanol as a new automobile fuel,[1] its availability, and thus the incidence of acute intoxication—whether accidental or deliberate—will likely increase. With methanol intoxication, rapid diagnosis and treatment is essential to prevent death and minimize the neurologic sequelae of poisoning.

In this review we describe the clinical and laboratory features of methanol poisoning, discuss the differential diagnosis and treatment of acute intoxication, and review the pathology and pathophysiology of the central nervous system (CNS) lesions associated with methanol ingestion.

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HISTORY

Poisoning with methanol was practically unheard of in the United States until 1890 when an inexpensive method of producing pure methanol was discovered.[2] Before that time, methanol produced by the dry distillation of wood had a bad taste and smell that made it unpalatable. With the new method of production, methanol was touted as a harmless and excellent substitute for the more expensive ethanol.[2] Although several hundred cases of intoxication were reported by the turn of the century, the toxicity of methanol continued to be

debated in the medical literature for the next 40 years.[2] Many investigators during this time believed that poisoning was due to impurities and not to methanol itself. Supporting this belief was the apparent failure of several researchers to induce toxic changes in laboratory animals by giving them pure methanol.[2]

Reif presented convincing evidence that pure methanol was indeed toxic in his analysis of the fluid responsible for a large outbreak of poisoning in Hamburg, Germany, in 1923.[3] He showed that the fluid contained less than 0.1% aldehydes, acetone, acids, and esters—concentrations too small to be toxic.[3] In addition, Reif found no cyanides and arsenics, which others had suggested were the offending compounds in so-called methanol poisoning.[3]

Even with Reif's documentation, many continued to doubt the toxic properties of methanol, mainly because of the marked variability in tolerance. There have been reports of some persons ingesting large amounts of methanol with no apparent ill effects, whereas others suffered permanent blindness after ingesting only a few teaspoonfuls.[2,4–7] Although the toxicity of methanol is now well accepted, this variability is still unexplained.

PHARMACOLOGY

Pure methanol is a colorless liquid that is easily absorbed through the gastrointestinal tract, skin, and respiratory tract.[4,8] The minimum lethal dose is about 80 g in untreated patients and visual defects can be expected with ingestion of half of this dose.[9] Methanol distributes readily in body water and may be concentrated in vitreous humor and cerebrospinal fluid.[10] A small amount is excreted unchanged by the lungs and by the kidneys.[8]

Methanol is oxidized by hepatic alcohol dehydrogenase at a rate about one-fifth that of ethanol.[11] The product of this oxidation is formaldehyde which is rapidly converted to formate.[12–14] The accumulation of formate corresponds to the development of metabolic acidosis and accounts for 50% to 100% of the observed drop in the bicarbonate ion.[15–17] Formate directly inhibits cytochrome oxidase; and as aerobic respiration is depressed, lactic acid accumulates, exacerbating the metabolic acidosis.[7,18,19]

It is formic acid and not methanol that is responsible for the acidosis and ocular damage in methanol intoxication.[12–14] The oxidation of methanol can be prevented by giving 4-methylpyrazole, an alcohol dehydrogenase inhibitor. In monkeys given 4-methylpyrazole, no acidosis or signs of toxicity develop despite toxic blood levels of methanol.[14,20] Formate infused into monkeys maintained at normal pH produces ocular lesions similar to those seen in methanol poisoning.[13]

TABLE 1
CLINICAL FEATURES OF METHANOL INTOXICATION

Mild central nervous system depression
Visual disturbances
Severe epigastric pain
Weakness
General feeling of ill being
Memory loss
Confusion
Agitation
Stupor
Coma

The metabolism of formate in man is still unclear. In some animals, such as the rat, formate is rapidly converted to carbon dioxide via a folate-dependent one-carbon pathway.[21] Because this pathway is efficient, these animals do not develop acidosis after ingesting methanol. However, if rats are made folate-deficient, they are unable to use this pathway. Formate accumulates, and a toxic state develops that is identical to that in man.[22] Hepatic tetrahydrofolate levels are 40% lower in monkeys than in rats, corresponding to the 50% lower rate of formate oxidation observed in monkeys.[23] Thus, the susceptibility of monkeys and possibly humans to methanol toxicity may be related to a relatively low level of hepatic tetrahydrofolate.[23]

Noker and associates reversed the toxic effects of methanol in monkeys by administering folinic acid, a folate derivative. Folinic acid decreased or prevented accumulation of formic acid and was effective when given both at the same time methanol was given and after toxicity developed.[24] This study suggests that folinic acid may be useful in treating methanol intoxication in humans.[24]

CLINICAL FEATURES OF METHANOL POISONING

The clinical features of acute methanol poisoning have been thoroughly described by Bennett and coworkers, who reviewed an outbreak in Atlanta involving 323 people.[4] Typical features are listed in *Table 1*.

Symptoms

Methanol has a central nervous system depressant effect similar to ethanol. There is a characteristic latent period which corresponds to the slow conversion of methanol to formate. Symptoms usually develop 24 hours after ingestion, but may appear as soon as 12 hours. Initially there is a general feeling of ill being with weakness, headache, and nausea. There may be severe

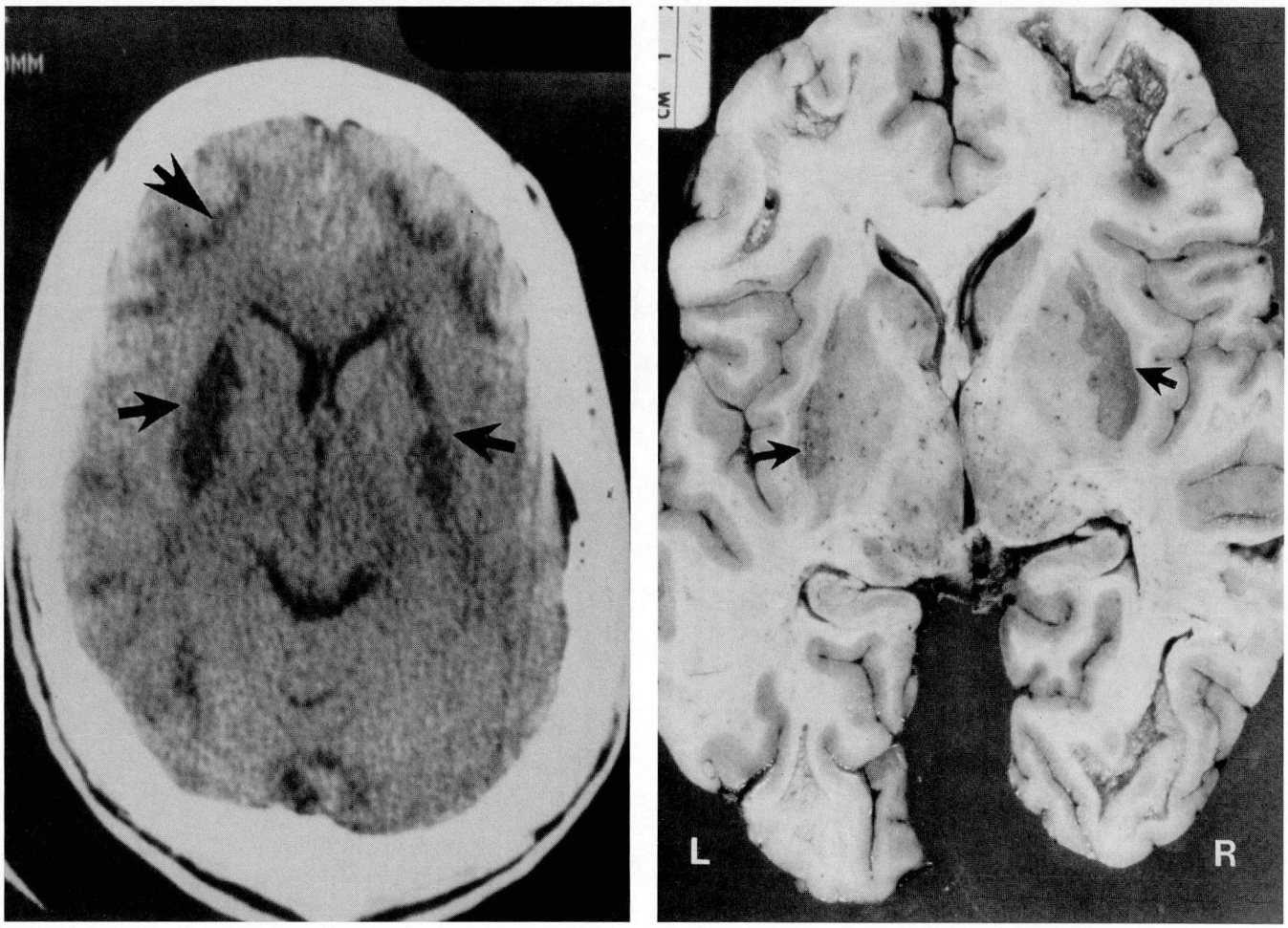

FIGURE 1. CT scan (left) and corresponding brain section (right) from 25-year-old male who died 17 days after ingesting methanol-containing tar and bug remover. The characteristic bilateral putaminal necrosis is seen on CT as symmetrical areas of low attenuation (arrows). Also, the areas of subcortical white matter necrosis are apparent on the CT scan (arrows).

epigastric pain similar to that described in acute pancreatitis.[4,25,26] As acidosis develops, most patients complain of visual disturbances. They usually describe blurred or misty vision, double vision, or changes in color perception. There may be constricted visual fields and, occasionally, total loss of vision.[4,27] Other central nervous system symptoms correlate with the severity of the developing acidosis. There may be mild to profound loss of memory, confusion, and agitation which progresses to stupor and coma as the severity of the acidosis increases.[4]

Physical examination

Patients may be apprehensive or combative. The vital signs are usually normal and Kussmaul type respirations are uncommon despite severe acidosis.[4] Patients with severe abdominal pain may have rigidity of the abdominal wall but rebound tenderness is not seen.[4,22]

The ophthalmologic exam is abnormal in most patients. Even patients without visual impairment will exhibit dilated and sluggish or nonreactive pupils.[27,28] These ophthalmoscopic changes are characteristic, and their severity correlates with the degree of acidosis. Occasionally, retinal changes are present in nonacidotic patients.[4,27] The earliest finding is hyperemia of the optic disc which may be striking and lasts up to 3 days.[4,27,28] Peripapillary retinal edema and optic disc edema develop more slowly and may persist for up to 2 weeks.[4,27] In cases of severe toxicity, optic atrophy may develop.[4,28]

TABLE 2
LABORATORY FINDINGS OF METHANOL INTOXICATION

Increased methanol level
Increased formic acid
Metabolic acidosis
Increased anion gap
Increased osmolal gap
Increased lactic acid
Increased amylase
Increased mean corpuscular volume

Laboratory findings

The laboratory findings are summarized in *Table 2*. A definitive diagnosis depends on identifying methanol and formic acid in blood or urine. A severe metabolic acidosis is present with a high anion gap and elevated osmolal gap.[29] Lactic acid may be elevated. Sodium and potassium are initially normal. Urinalysis is normal and no crystals are present in the sediment.[4] The hemoglobin, hematocrit, and white blood cell count are normal, but the mean corpuscular volume may be elevated. This finding is probably a reflection of general cellular swelling and has been used as an indication of more severe toxicity.[26] Serum amylase may be elevated, indicating acute pancreatitis.[4,25]

Computed tomographic scan

Symmetrical putaminal necrosis is a common finding at autopsy in patients with methanol intoxication.[9,30] These lesions can be detected on computed tomographic (CT) scan as early as 3 days after ingestion, and appear as areas of low attenuation which may extend into the surrounding white matter (*Figure 1*).[31–33] Aquilonius and associates correlated CT findings with prognosis in six patients with methanol poisoning and suggested that the diagnosis be considered when putaminal lesions are identified on CT even if blood methanol is undetectable.[31,32]

PATHOLOGY

At autopsy, the most common finding is cerebral edema, which is often marked.[4,34] Other common findings include pulmonary edema and hemorrhagic gastritis.[34] Acute hemorrhagic pancreatitis is common in those patients who had epigastric pain.[4] In patients with prolonged survival, complications of coma and intubation, including pneumonia and pulmonary emboli, are not unexpected.

Extensive central nervous system abnormalities have been described in methanol poisoning.[35,36] Methanol is selectively toxic to the optic nerve and basal ganglia and causes characteristic lesions in these areas. In the optic nerve, there is selective demyelination of the retrolaminar segment, consisting of central demyelination beginning directly behind the lamina cribrosa and extending proximally for several millimeters.[36] On cross section, a rim of spared myelin is present around the demyelinated core (*Figure 2*). Axons are preserved, although axonal swelling is often significant.[36,37] Proximal to the lesion, myelination is normal.[36]

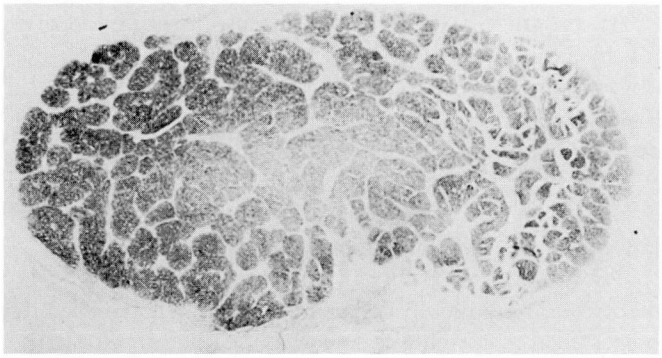

FIGURE 2. Cross-section of optic nerve (stained with Luxol fast blue) from patient who died of methanol intoxication. There is a central core of pallor corresponding to the area of demyelination, with a surrounding rim of spared myelin.

Ocular changes

Electron microscopic examination of optic nerves from methanol-poisoned rhesus monkeys showed generalized swelling of intra-axonal mitochondria and clear spaces within the myelin sheath in the retrolaminar portion.[37] Early reports emphasized degeneration of ganglion cells of the retina with sparing of the optic nerve.[34,38–40] Most investigators now believe the ganglion cell changes represented artifact, and that these patients died before the optic nerve lesion had time to develop.[36]

Theories of the pathogenesis of visual loss in methanol poisoning must be able to explain all of the observed changes including optic disc edema, visual dysfunction, and selective demyelination of the retrolaminar optic nerve. Based on their experiments with rhesus monkeys, Hayreh and co-workers believe that the direct toxic effect of formate is responsible for the ocular changes.[28,37] Since formate inhibits cytochrome oxidase, adenosine triphosphate (ATP) production is inhibited and ATP-dependent functions are depressed.[18,19] The loss of the sodium-potassium membrane pump inhibits electrical conduction, causing the early, but potentially reversible, visual disturbances.[28,37]

Anterograde axoplasmic flow is also inhibited, resulting in axonal swelling and optic disc edema.[28,37] Since oligodendroglial cells are particularly sensitive to the loss of membrane functions, they also swell and compress adjacent axons, further inhibiting axoplasmic flow. As the oligodendroglia are further damaged, there is eventual demyelination, loss of saltatory conduction, and permanent visual damage.[36]

The unique sensitivity of the retrolaminar nerve segment is not completely understood. Sharpe and associates suggested that formate is selectively concentrated in the optic nerve head.[36] This area receives its blood supply from the peripapillary choroid vessels, and flow through these vessels is estimated to be two to three times that of the renal cortical blood flow.[41] In addition, the optic nerve is bathed by cerebrospinal fluid and formate is concentrated there.[10] Alternatively, Sharpe and colleagues proposed that decreased blood perfusion may exacerbate the effects of formate on the optic nerve head.[36] This area is a vascular watershed and a similar pattern of demyelination occurs here after profound hypotensive episodes.[41–43]

Putaminal and white matter necrosis

Bilateral hemorrhagic putaminal necrosis appears to be unique to methanol intoxication. There may be involvement of only a small area of the putamen, or hemorrhage and necrosis may involve the entire putamen with extension into the surrounding white matter (*Figure 1*).[32,35] The mechanism for this selective necrosis is difficult to explain. Perhaps formate is concentrated in this area secondary to decreased venous drainage.[35] It is interesting that carbon monoxide, which also inhibits cytochrome oxidase, causes necrosis of the globus pallidus while sparing the putamen.[44] A rare Parkinsonian-like extrapyramidal syndrome has been described in survivors of methanol poisoning and may be related to the putaminal necrosis.[33,45] Although most reported cases with documented putaminal necrosis do not have symptoms attributable to this lesion, the symptoms and signs may have been subtle and overlooked.[45]

Extensive white matter necrosis has been described in methanol intoxication [35] and in a variety of other conditions, including carbon monoxide poisoning, postoperative and postanesthesia hypotensive episodes, and after strangulation attempts.[46,47] Common to all these conditions is the simultaneous occurrence of cerebral edema and hypoxia.[47] The pattern of necrosis is characteristic, with sparing of the subcortical arcuate fibers (*Figure 3*). These lesions have been documented by CT.[35]

Burger and Vogel suggested that the differences in the vasculature of the grey and white matter lead to the selective white matter necrosis.[46] The grey matter and the subcortical white matter are supplied by a rich, branching capillary network arising from pial vessels.[48,49] The venous drainage from these areas is external, via the pial vessels.[50] The deeper white matter is supplied by longer and larger caliber vessels which pass through the cortex without branching.[48,49] Venous drainage from the white matter is internal, to the Galenic system.[50]

Diffuse cerebral edema would compress and compromise both the arterial supply and the venous drainage of the deep white matter while the grey matter and the subcortical arcuate fibers would continue to be perfused via their rich anastomosing blood supply.[46] In

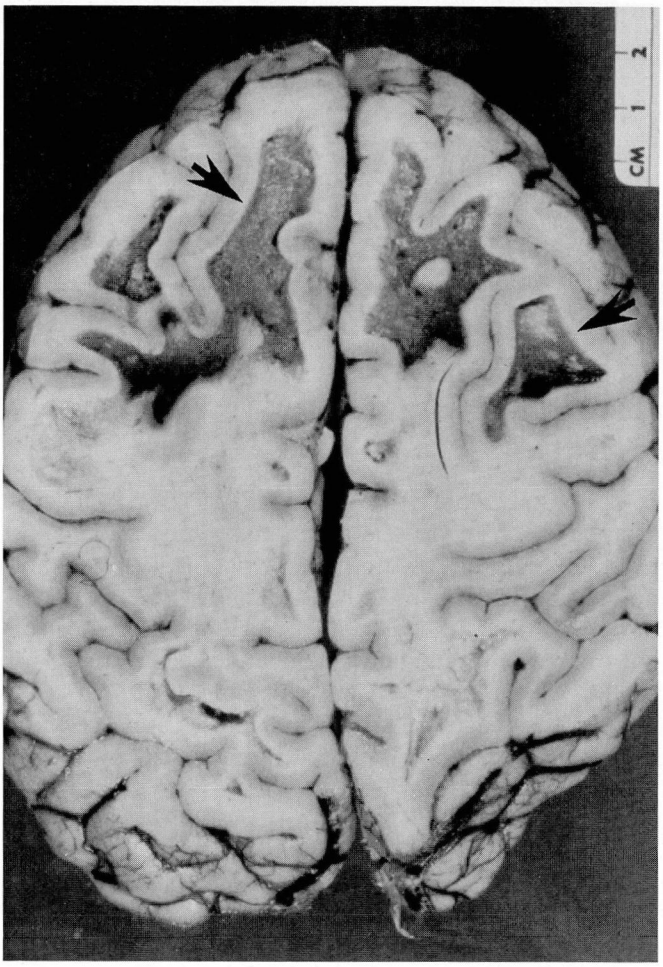

FIGURE 3. Brain section from same patient as Figure 1. There are large areas of white matter necrosis with sparing of the subcortical arcuate fibers (arrows).

TABLE 3
CAUSES OF INCREASED ANION GAP ACIDOSIS*

Uremia
Ketoacidosis
Lactic acidosis
Salicylate
Methanol
Ethylene glycol
Paraldehyde

* [Na+] - ([HCO3-] + [Cl-]) > 15 mmol/L

TABLE 4
CAUSES OF INCREASED OSMOLAL GAP*

Methanol
Ethyl ether
Isopropanol
Ethylene glycol
Acetone

$$*\text{Osmolal}_{\text{measured}} - (1.86\,[Na^+] + \frac{BUN}{2.8} + \frac{[Glucose]}{18}) > 5\text{mOsm/kg}$$

addition, the long penetrators supplying the deep white matter may be more sensitive to hypoxia-induced vasospasm, further compromising the blood supply.[46] With aggressive therapy and prolonged respirator use, these white matter lesions may dominate and lead to severe neurologic sequelae.[35]

DIFFERENTIAL DIAGNOSIS

Rapid diagnosis of methanol intoxication is essential, since treatment must begin immediately. The diagnosis must be suspected in any patient who complains of visual disturbances, is confused or agitated, or has an unexplained metabolic acidosis.[29]

Although a definitive diagnosis depends on identifying methanol or formate in blood or urine, these assays may not be available on a 24-hour basis. In these situations, the differential diagnosis of unexplained metabolic acidosis can be narrowed by determining the anion and osmolal gap, thus allowing appropriate therapeutic intervention.[29,51,52]

Anion gap

The anion gap is determined by calculating the difference between sodium and the measured serum anions, chloride and bicarbonate (*Table 3*).[29,52] The normal anion gap of about 14 mmol/L is accounted for by proteins, sulfate, phosphate, and organic acids.[29,52] An increase in any unmeasured anion will elevate the anion gap. *Table 3* lists the differential of a high anion gap. In methanol poisoning, the accumulation of formate causes the high gap.[29]

Osmolality

Osmolality is a reflection of the number of molecules dissolved in a solute.[53] The serum osmolality can be quickly calculated using the following formula[53]:

$$\text{Osmolal} = 1.86\,[Na^+] + \frac{BUN}{2.8} + \frac{[Glucose]}{18}$$

The osmolal gap is the difference between the measured and calculated osmolality and normally is less than 5 mOsm/kg.[29,53] Any substance dissolved in serum elevates the osmolal gap; however, only those present in high molar concentrations cause a significant increase.[29] Agents capable of raising the osmolal gap are listed in *Table 4*. Of the suspected toxic ingestions, only methanol and ethylene glycol are capable of raising both the anion gap and the osmolal gaps.[29]

Methanol *v* ethylene glycol

Distinguishing methanol from ethylene glycol intoxication in a stuporous or comatose patient presenting to the emergency room may not be possible initially.[51] Like methanol, ethylene glycol is a popular substitute for ethanol and may be ingested deliberately or accidentally.[51,54,55] Ethylene glycol is metabolized to toxic products by alcohol dehydrogenase, and accumulation of these products causes a metabolic acidosis.[51] There is an asymptomatic latent period as in methanol poisoning, and neurologic symptoms may be present.[54] The presence of oxalate crystals in the urine supports a diagnosis of ethylene glycol ingestion but crystals may not be present in all cases.[51,54,56] Because prognosis in both methanol and ethylene glycol intoxication depends on prompt treatment, the osmolal and anion gap should be determined on any patient presenting with a metabolic acidosis of unknown etiology. If both gaps are elevated, therapy should be initiated while awaiting blood levels to confirm the diagnosis.

TREATMENT

Treatment is aimed at reversing the metabolic acidosis, removing methanol and formate, and preventing further oxidation of methanol to formate.[2,4,6,9,57]

Rapid reversal of the metabolic acidosis is probably the most important measure in acute intoxication.[4] Sodium bicarbonate should be administered intravenously to maintain a blood pH above 7.35.[26] The correction of the bicarbonate deficit is often associated with a dramatic improvement in visual disturbances, pain, and mental status. Coma may be reversed as the acidosis is corrected but, unfortunately, the improvement may be temporary.[4]

Hemodialysis is effective in rapidly removing both methanol and formate.[9,57] It should be initiated in any patient whose blood methanol level is greater than 50 mg/dL or who has ingested a large amount of methanol, is severely acidotic, or has visual symptoms.[6,57,58] If the methanol ingestion was recent, gastric lavage may help prevent further absorption.[4]

Ethanol has been used in the treatment of methanol poisoning since the turn of the century.[2] Patients who have ingested both methanol and ethanol tend to have fewer symptoms, less severe visual damage and increased survival.[2,58] Ethanol competes with methanol for alcohol dehydrogenase. Since this enzyme preferentially binds ethanol, the oxidation of methanol to formate is depressed.[11,59]

Although ethanol is effective in preventing acidosis and ocular toxicity, there are a number of problems associated with its use. Since ethanol is rapidly eliminated and is removed during hemodialysis, blood levels must be continually monitored and dosages adjusted to maintain a blood level of 100 mg/dL.[6,26] In addition, the CNS-depressant side effects of ethanol are undesirable in critically ill patients.

Currently under study as an alternative to ethanol therapy is 4-methylpyrazole (4-MP). 4-MP is a potent inhibitor of alcohol dehydrogenase rather than a competitive substrate as is ethanol.[60,61] The drug can be given intramuscularly or orally, has few CNS side effects at therapeutic levels and is slowly metabolized and eliminated.[60,61] 4-MP has proven to be effective and safe when given to methanol-intoxicated monkeys[61–63] and has been successfully used to treat ethylene glycol intoxication in humans.[64] This drug is currently undergoing clinical trials in humans and should prove to be an effective therapy for methanol and ethylene glycol toxicity as well as severe disulfiram-ethanol reactions.[62]

PROGNOSIS

Predicting outcome is difficult on an individual basis because of the marked variability in tolerance to methanol. Survival correlates best with the severity of the metabolic acidosis and the length of time before it is corrected. The amount of methanol ingested and the blood methanol level are less useful parameters than the degree of acidosis.[25,57,58] Although the initial methanol level is useful in predicting the severity of the intoxication,[26] a low serum methanol level with severe acidosis is evidence of advanced methanol oxidation and is a poor prognostic sign.[9] Prompt aggressive treatment increases survival even in markedly acidotic patients.[57] The concurrent ingestion of ethanol increases survival by delaying the development and degree of acidosis.[58]

Permanent visual damage, such as blurred vision, scotoma, or blindness, is present in up to 15% of survivors.[28] Marked and prolonged acidosis, severe initial visual symptoms, severe impairment of pupillary light reflex, and marked retinal edema indicate severe eye damage and poor prognosis.[27,57] Less common neurologic sequelae include a Parkinsonian motor disorder,[33,45] and peripheral neuropathy.[35]

ACKNOWLEDGMENT

The authors wish to thank Mrs. Denise Egleton for typing the manuscript, Drs. Lucy B. Rorke, Richard Welles, and Nicholas Zakov for contributing patient material, and Dr. Robert Cunningham for his review.

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