Alcohols intoxications

Ethanol Toxicity

Ethanol toxicity results from the ingestion of ethanol, usually in large quantities. This can occur from the ingestion of beverage ethanol, commonly known as alcohol, and non-beverage ethanol, present in substances such as mouthwash, cologne, and cough medicine. Alcohol is the most common form of ethanol and is a widely used and abused substance, mostly in western culture, representing the oldest and most widely abused substance. The demographic most likely to present for acute alcohol intoxication are adolescents and young adults.

Alcohol is absorbed through the proximal GI tract. It is primarily metabolized in the liver by alcohol dehydrogenase to acetaldehyde. The primary site of action in acute toxicity is the central nervous system, where it increases central nervous system (CNS) inhibition and decreases excitation. Alcohol binds strongly to GABA receptors, activating the inhibitory cascade, which results in sedation, cognitive dysfunction, and decreased coordination. With chronic use of alcohol, the number of GABA receptors is increased, requiring more and more alcohol to create the same level of inhibition. This is a phenomenon known as tolerance. This tolerance partly explains the alertness of chronic alcohol users at blood alcohol levels that in others would cause coma or death. Benzodiazepines also bind to the GABA receptor, making them useful in alcohol withdrawal. Alcohol also inhibits the primary excitatory neurotransmitter in the CNS, glutamate. Patients with alcohol use disorder have increased numbers of NMDA(N-methyl D-aspartate) receptors and increased sensitivity of these receptors to glutamate. Due to the increased sensitivity of these receptors, patients with alcohol use disorder are at risk for seizures and hallucinations when alcohol is withdrawn.

Criteria for diagnosis of alcohol intoxication include known or admitted ingestion of alcohol, change in behavior, clinical signs including slurred speech, incoordination, nystagmus, memory loss, and lack of another condition to account for the symptoms. The extent and severity of these symptoms vary depending on how quickly the alcohol is ingested. The speed of absorption can be affected by co-ingested food, female sex, cigarette use, and concentration

of alcohol in the beverage. It is important to ascertain the quantity and type of alcohol consumed and over which period of time it was consumed. Patients may complain of nausea, vomiting, and diarrhea. Acute alcohol intoxication can cause respiratory depression, establishing that the patient is protecting their airway is of primary importance.

Acute alcohol intoxication causes several metabolic abnormalities, including lactic acidosis, hypoglycemia, hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia. Laboratory analysis should include a full electrolyte panel as well as liver function tests. Alcohol can cause acute effects on the cardiovascular system, such as atrial and ventricular tachydysrhythmias. An EKG should be obtained. In the case of altered mental status, when a full history cannot be elucidated, a CT scan of the brain should be obtained to rule out any intracranial pathology that is contributing to the patients' mental status. Many intoxicated patients may state suicidal thoughts or make such gestures. A psychiatric evaluation should be performed and may have to be repeated as the patient becomes more lucid.

Treatment for acute ethanol toxicity is mostly supportive. The first priority, as always, is airway protection. The main life-threatening complication of alcohol intoxication is respiratory depression. Alcohol does act as a diuretic; thus, most patients who receive intravenous fluids are in an attempt to treat dehydration. Checking a point of care glucose is important as many patients with alcohol use disorder will have depleted glycogen stores, and treating hypoglycemia is important, especially before replenishing vitamins such as thiamine. Patients with alcohol use disorder may not benefit from IV fluids, and the consideration must be made for alcoholic cardiomyopathy in this patient population before the administration of fluids. Some patients may become agitated or violent. In these situations, sedative substances may be required, including droperidol or haloperidol, keeping in mind the potential interaction between the drug and alcohol.

Methanol Toxicity

Methanol (CH3OH) is a toxic alcohol that is found in various household and industrial agents. The term “toxic alcohols” is a collective term that includes methanol, ethylene glycol, and isopropyl alcohol. Methanol exposure can be extremely dangerous, with significant morbidity and mortality if left untreated. Methanol poisoning is most often due to accidental or intentional ingestions, and accidental epidemic poisonings due to distilling and fermenting errors and beverage contamination. Products that contain methanol include windshield washer fluid, gas line antifreeze, carburetor cleaner, copy machine fluid, perfumes, food warming fuel and other types of fuels.

When ingested, methanol is absorbed rapidly via the gastrointestinal tract in less than 10 minutes. Methanol is not protein-bound and is absorbed directly into the total body water compartment with a volume of distribution of approximately 0.7 L/kg. Serum concentrations peak immediately after absorption and follow a zero-order elimination rate. Metabolism occurs mainly in the liver through serial oxidation via alcohol dehydrogenase and aldehyde dehydrogenase but begins with alcohol dehydrogenase present in the gastric mucosa. Alcohol dehydrogenase oxidizes methanol to formaldehyde, and aldehyde dehydrogenase subsequently oxidizes formaldehyde to formic acid. Each of these two oxidation steps is associated with a reduction of NAD(nicotinamide adenine dinucleotide) to NADH. Formic acid is not easily eliminated and mostly accumulates, while a small amount in its unprotonated form, formate, interacts with folate to create carbon dioxide and water for exhalation. Unmetabolized methanol is not sufficiently cleared through the kidneys or the lungs and has an effective half-life of about 30 to 85 hours.

A potentially lethal dose of methanol is approximately 30 to 240 mL or 1 gram per kilogram. Permanent visual damage may occur with a minimum ingestion of 30 mL of methanol. The parent compound, methanol, accounts for the increased osmolality. Formic acid is the primary toxic metabolite that accounts for the associated anion gap metabolic acidosis and end-organ damage. Therefore, as methanol is metabolized, the osmolar gap decreases and the anion gap increases. Development of an anion gap metabolic acidosis associated with formate accumulation is multifactorial, due to the accumulation of organic acids that are not easily eliminated (for example, formic acid and formate), and the disruption of oxidative phosphorylation due to formate’s inhibition of cytochrome oxidase. Formate’s hindrance of mitochondrial respiration can also cause a degree of lactatemia, which can enhance formate’s ability to cross the blood-brain barrier as formic acid.

Lactate is also elevated secondary to enhanced shunting of pyruvate to lactate from the increased NADH/NAD ratio associated with alcohol metabolism. End organ damage and retinal toxicity are primarily due to formic acid's oxidative stress.

History is often challenging to acquire in an intentional, self-harm attempt or substance abuse scenario and physical exam can often be normal in early ingestions.

Patients who present within the first 12 to 24 hours following ingestion may appear normal, and this is described as the latent period. Nausea, vomiting, and abdominal pain subsequently ensue, followed by central nervous system (CNS) depression and hyperventilation as metabolic acidosis occurs. Ocular symptoms associated with retinal toxicity are often evident in the form of blurry vision, decreased visual acuity, photophobia, and "halo vision." These symptoms are associated with physical exam findings that may include papilledema, optic disc hyperemia, and pupillary defects on fundoscopic evaluation. Without treatment, patients may progress to coma, respiratory or circulatory failure and death.

A patient who has ingested methanol will present somewhere along the spectrum of asymptomatic with an increased osmolar gap to very ill with end-organ toxicity and anion gap metabolic acidosis.

Toxic alcohol concentrations are confirmatory and are measured by gas chromatography, which is not readily available in all healthcare facilities. Concentration is reported in milligrams per deciliter (mg/dL) and, since it typically peaks soon after absorption, is expected to decrease by zero-order kinetics. The time of ingestion is also important to consider, as the toxic alcohol concentration may not reflect the level of toxicity if metabolism has already progressed because the metabolites are primarily responsible for the toxic effects. In the case of methanol, a formate concentration may be assessed to correlate with acidosis or any clinical findings of end-organ damage.

When methanol toxicity is being considered in a patient presenting with an anion gap metabolic acidosis, the patient should be screened for the aforementioned associated symptoms, particularly visual disturbances and a funduscopic exam should be performed. In addition, when a serum methanol

concentration cannot be confirmed, it is especially important to rule out salicylate toxicity.

Treatment options for methanol toxicity include supportive care, fomepizole (Antizole, 4-Methylpyrazole or 4MP), ethanol, dialysis and theoretically, folate. Fomepizole is the antidote for toxic alcohols, and its mechanism of action is the inhibition of alcohol dehydrogenase. Ethanol may also be utilized therapeutically to inhibit alcohol dehydrogenase when fomepizole is unavailable. There are advantages and disadvantages to either treatment. Fomepizole is more easily dosed, does not cause any inebriation, strongly inhibits alcohol dehydrogenase, but is fairly expensive. Ethanol is less expensive but is harder to dose accurately, requires close monitoring of the serum ethanol concentration, and causes inebriation that may necessitate intensive care monitoring.[1][4]

Indications for treatment include an elevated methanol concentration and severe or progressing acidosis, despite resuscitation, with clinical suspicion of methanol ingestion.

Fomepizole or ethanol serve as alcohol dehydrogenase inhibitors to stop the conversion of methanol to its toxic metabolite, formate. When alcohol dehydrogenase is inhibited, clearance of methanol is prolonged from approximately 8.5 mg/dL/hr to an effective half-life of 45 to 90 hours. Fomepizole is given intravenously, with a loading dose of 15 mg/kg, and then maintenance dosing of 10 mg/kg every 12 hours for 4 doses or until the methanol concentration is less than 32 mg/dL with a normal acid-base status. If additional dosing is required beyond 4 maintenance doses, then dosing increases to 15 mg/kg every 12 hours due to autoinduction of increased metabolism. During dialysis, fomepizole should be dosed every 4 hours as it is dialyzable.

Dosing of ethanol is more complicated, difficult to monitor, and has the added side effect of inebriation. Ethanol may be given intravenously or orally. However, it should only be given if fomepizole is unavailable as it would be inappropriate to cause the patient to be inebriated for such an extended period. When treating with ethanol, the goal therapeutic serum concentration is a range of 80 to 120 mg/dL. Intravenous ethanol formulary is usually 10%, and a loading dose is calculated using the product of the goal plasma

concentration (C = 100mg/dL), the volume of distribution of ethanol (V = 0.6L/kg), and the patient's weight. Maintenance dosing is then based on elimination rate. Empirically, 10% intravenous ethanol may be administered with a loading dose of 8 mL/kg over 30 to 60 minutes, followed by maintenance dosing of 1 to 2 mL/kg per hour. Maintenance dosing is doubled during dialysis. Oral dosing may be calculated using the above equation for serum alcohol concentrations by using 100 mg/dL for the serum concentration and then solving for the amount ingested. Empirically, 50% (100 proof) oral ethanol may be administered with a loading dose of 2 mL/kg followed by 0.2 to 0.4mL/kg per hour. Maintenance dosing is doubled during dialysis.

Patients with a toxic methanol ingestion should be strongly considered for hemodialysis. Due to its low volume of distribution and lack of protein-binding, both methanol and the toxic metabolite, formate, are dialyzable. Hemodialysis is often beneficial for methanol toxicity because it can significantly decrease the patient's length of stay. Once alcohol dehydrogenase is inhibited, clearance of methanol is prolonged from approximately 8.5 mg/dL per hour to an effective half-life of 45 to 90 hours. However, the only absolute indication for hemodialysis in methanol toxicity is new visual impairment in the presence of metabolic acidosis. Relative indications for hemodialysis include methanol concentration greater than 50 mg/dL, severe metabolic acidosis refractory to resuscitation, history of ingestion of a lethal dose of 1gm/kg, renal failure, and other standard indications for dialysis.

Additional treatment of methanol toxicity includes folate. Folate administration is of theoretical benefit as it may enhance the metabolism of the toxic metabolite, formate, to carbon dioxide and water.

Ethylene Glycol Toxicity

Ethylene glycol ($C_2H_6O_2$) is a toxic alcohol that is found in various household and industrial agents. Ethylene glycol exposure can be extremely dangerous, with significant morbidity and mortality if left untreated. Ethylene glycol is a colorless, sweet-tasting liquid most commonly found in antifreeze, but occasionally used for other purposes, such as industrial solvents. Exposures are generally observed due to accidental or intentional ingestions, with its

sweet taste lending to accidental toxic exposures, whereas intentional exposures may be motivated by suicide attempt or desire for inebriation in the absence of ethanol.

Ethylene glycol is rapidly absorbed through the gastrointestinal tract after ingestion with serum concentrations peaking very soon after ingestion. Elimination is primarily first order when concentrations are under 250 mg/dL, with a half-life of approximately 4-6 hours.[5] With concentrations above 250 mg/dL, elimination becomes zero order at likely around 10 mg/kg/hr.

Like ethanol and methanol, metabolism begins with gastric mucosal alcohol dehydrogenase, and occurs primarily in the liver through serial oxidation by alcohol dehydrogenase and aldehyde dehydrogenase, with each step reducing NAD+ to NADH. Ethylene glycol is first oxidized by alcohol dehydrogenase to glycoaldehyde, which is then oxidized by aldehyde dehydrogenase to glycolic acid, which is primarily responsible for the associated metabolic acidosis. Glycolic acid is then oxidized to glyoxylic by glycolic acid oxidase, or lactate dehydrogenase due to its resemblence of lactate. Glyoxylic acid is a precursor for oxalic acid, the nephrotoxic metabolite;

A potentially lethal dose of ethylene glycol is approximately 1-2 mL/kg of 95% concentrated solution, or about 1,500 mg/kg. Ethylene glycol's metabolites are responsible for the anion gap metabolic acidosis. it is glycolic acid that is believed to be long-lived enough to be primarily responsible for the anion gap metabolic acidosis, while oxalic acid is responsible for the associated end-organ injury, nephrotoxicity. Oxalic acid deposits in renal tubules as insoluble calcium oxylate monohydrate, leading to proximal tubular necrosis. Oxalic acid's affinity for calcium may lead to hypocalcemia, which can be associated with tetany, seizures, and QT interval prolongation on electrocardiogram.

Severity of illness will vary with time from exposure to presentation, if coingestion of ethanol has occurred, or if early treatment was accessible. Ethylene glycol toxicity usually presents with a varying degree of inebriation early in the course, with the potential for central nervous system depression (CNS). During this time, there is often an elevated osmolar gap without an elevated anion gap or acidosis. As the concentration of ethylene glycol shifts toward production of metabolites, the osmolar gap decreases and the anion gap increases with the development of a metabolic acidosis. Ingestion of ethanol at any point will halt the metabolism of ethylene glycol. As ethylene

glycol is progressively metabolized over the course of 4-12 hours, an anion gap metabolic acidosis develops secondary to the accumulaiton of glycolic acid. During this time, the patient may feel generally ill or be CNS depressed, and may begin to compensate with hyperventilation or hyperpnea. Tachycardia and hypertension may also occur. After about 12 hours, there may be evidence of nephrotoxicity, demonstrated by elevated creatinine, due to the precipitation of calcium oxalate crystals in the proximal tubules. This caclium oxalate deposition may predisopose to hypocalcemia, placing patient at risk for tetany, seizures, QT interval prolongation and dysrhythmias. After about 12-18 hours, oliguira may develop. If treatment occurs during this time, the acute renal injury is normally reversible and dialysis is often unnecessary. However, if treatment is delayed further, usually by delayed presentation or recognition, acute renal failure and systemic illness may develop, including acute respiratory distress syndrome, cerebral edema or infarction, and heart failure.

Toxic alcohol exposure is confirmed when a serum concentration demonstrates the diagnosis. Other findings that may be present in ethylene glycol toxicity may include urinary calcium oxylate crystals, serum hypocalcemia secondary to precipitation of caclium oxylate crystals, QT interval prolongation on electrocardiogram as a result of said hypocalcemia, and elevated or falsely elevated lactate as a result of assay interference from glycolic acid.

Treatment options for ethylene glycol toxicity include supportive care, fomepizole (Antizole, 4-Methylpyrazole or 4MP), ethanol, dialysis and theoretically, thiamine, pyridoxine and magnesium. Fomepizole is the antidote for toxic alcohols, and it acts by inhibiting alcohol dehydrogenase to cease toxic alcohol metabolism. Ethanol may also be utilized therapeutically to inhibit alcohol dehydrogenase when fomepizole is unavailable.

Ethylene glycol and its metabolites are dialyzable; however, with proper administration of fomepizole, dialysis is generally not indicated in the absence of renal dysfunction. Unlike methanol or diethylene glycol, fomepizole alone is the recommended treatment for a toxic exposure to ethylene glycol without renal dysfunction, and only minimal acid-base disturbances, as it is far less likley that any toxicity is associated with unmetabolized ethylene glycol. The effective half life of ethylene glycol is only increased to about 17 hours when alcohol dehydrogenase is inhibited; therefore, dialysis does not necessarily decrease length of stay either. Furthermore, its use often requires being in the intensive care unit in many hospitals, thus increasing costs. Hemodialysis

should be strongly considered in the presence of renal dysfunction, severe metabolic acidosis and severe electrolyte abnormalities. Normal urinary output needs to be assured to treat with fomepizole alone so that ethylene glycol can be reliably excreted. The presence of severe acidosis indicates the active and likely incomplete metabolism of ethylene glycol, with the concern that circulating glycolic acid may be converted to oxalate, which increases the risk of worsened renal function. Continuous renal replacement, although less effective, therapy may be considered if intermittent hemodialsyis is not feasible, particularly in the setting of hemodynamic instability. The decision to utilize hemodialysis is complicated and should be made in consultation with a medical toxicologist.

Additional treatment options may also be considered. Sodium bicarbonate infusion may be helpful, particularly in severe metabolic acidosis, but is not universally considered a standard recommendation. Calcium gluconate may be indicated if complications occur as a result of hypocalcemia, but should otherwise be replaced cautiously and judiciously as exogenous calcium administration may enhance the precipitation of calcium oxylate crystals. Seizures in the presence of hypocalcemia should be treated with benzodiazepines. Theoretically, administration of thiamine and pyridoxine and magnesium may assist in shunting glycolic acid metabolism away from oxalic acid and toward its nontoxic metabolites, α-hydroxy-β-ketoadipic acid and glycine, respectively, utlizing the mechanism discussed in the pathophysiology section.