

Ethylene Glycol

History

Ethylene glycol (EG) is the dihydroxy alcohol derivative of ethane. It was originally prepared in 1859 and used as a coolant and ingredient in explosives in World War I. In the 1930's EG production increased due to cheaper production methods. This in turn, led to the increased use of EG as an engine coolant since EG is a more efficient coolant than evaporative water cooling. While EG is most often encountered in various antifreeze solutions and coolants, it is also incorporated into solvents, industrial humectants, brake fluid, paints and lacquers, glass cleaners, and cosmetics. Ingestion of as little as one mouthful of a 99% EG antifreeze solution by either a child or adult may lead to toxic signs and symptoms. The lethal dose in adults is 1-1.5 mL/kg.

Mechanism of Action

Ethylene glycol's major toxicities are a result of it being metabolized to toxic metabolites. However, even without being metabolized, EG may cause symptoms of inebriation and CNS toxicity. The first enzyme in the metabolic pathway of EG is alcohol dehydrogenase. By blocking the action of this enzyme, the production of toxic metabolites can be stopped. When EG is metabolized by the body, it produces four toxic metabolites: glycoaldehyde, glycolate, glycolic acid, and glyoxylate. These metabolites cause (1) tissue destruction, primarily from calcium oxalate crystal deposition, and (2) metabolic abnormalities, specifically a high anion-gap metabolic acidosis, lactic acidosis, and hypocalcemia. Oxalic acid combines with calcium to form calcium oxalate crystals, which deposit in the kidneys. This can result in hypocalcemia, hematuria, and proteinuria, increased creatinine and renal failure.

Alcohol Dehydrogenase

Ethylene Glycol -----> Glycoaldehyde --> Glycolate --> Glyoxylate --> Oxalate

Kinetics

This clear, colorless, sweet-tasting liquid is rapidly and completely absorbed upon ingestion with peak blood levels occurring in 1-4 hours. It has a half-life of 2.5 to 4.5 hours; the half life may be extended to as long as 17 hours in the presence of therapeutic blood ethanol levels (100-200 mg/dL). Ethylene glycol has a volume of distribution (0.54-0.8 L/kg) similar to that of total body water. Ethylene glycol is filtered by the renal glomeruli and is passively reabsorbed. Approximately 20% of ethylene glycol is excreted unchanged in the urine.

Clinical Symptoms

Phase 1 (Minutes – 12 hours): CNS toxicity predominates with inebriation (without odor of ethanol on the breath), coma, nystagmus, paralysis, and seizures. Nausea, vomiting, and papilledema may also occur. An elevated serum osmolarity is seen early in this phase. Calcium oxalate crystals may be present.

Phase 2 (12-24 hours): Cardiopulmonary symptoms predominate with mild tachycardia and hypertension. Other effects include anion gap metabolic acidosis (possibly severe) with compensatory hyperventilation, hypoxia, CHF, and ARDS.

Phase 3 (>24 hours): This renal phase is characterized by acute tubular necrosis and renal failure. Oliguria, anuria, hematuria, and proteinuria are common.

Treatment

Triage: Any ingestion which is intentional or malicious needs to be referred to emergency department. Any patient showing signs or symptoms that might appear to be signs of inebriation need to be referred to emergency department. The concentration of the product is important in determining potential toxicity. If the concentration is >20% then a mouthful could be toxic, and in children anything more than a witnessed taste or lick may be a cause for concern.

Decontamination is generally of little value since EG is so rapidly absorbed from the GI tract. However lavage may be beneficial if performed within 60 minutes of a large ingestion.

Monitoring and Labs: Ethylene glycol levels are done by a relatively few laboratories so an excessive delay may occur before the hospital receives the laboratory results. If EG levels are not available within a few hours, treatment should be initiated until the lab results become available. Ethylene glycol levels > 20 mg/dL are considered toxic, but levels < 20mg/dL may still indicate a toxic amount of EG has been ingested if significant time has passed since the ingestion.

Serum osmolality, measured by freezing point depression, may be useful if ethylene glycol levels can not be done in a timely manner. A significantly elevated serum osmolality can be indicative of an EG ingestion. *However, the absence of an elevated serum osmolality does not rule out the ingestion of a toxic alcohol.* An elevated serum osmolality may be present within the first hour of ingestion as this is a result of the presence of EG itself, not the toxic metabolites, in the serum. As metabolism decreases the ethylene glycol concentration, the serum osmolality will decrease despite worsening systemic toxicity.

Electrolytes may be used to determine the presence of an anion gap. A normal anion gap is 8-16 mEq/L. *Absence of an anion gap does not rule out the ingestion of a toxic alcohol.* The anion gap is mainly due to a decrease in serum bicarbonate levels and usually follows the development of acidosis which typically develops within 12 hours of ingestion.

Renal function tests and urinalysis should be done on symptomatic patients. The presence of calcium oxalate crystals in the urine may help support the diagnosis of EG ingestion. However, the monohydrate form of calcium oxalate crystals are similar to sodium urate crystals and either crystal may be mistaken for the other.

Some brands of radiator antifreezes contain fluorescein, a dye that fluoresces under ultraviolet light. Urine or emesis from a patient who has ingested an automotive product with fluorescein may exhibit this fluorescence. However, this effect is NOT diagnostic as both false positive and false negative results can be obtained.

Management: Indications for antidotal therapy can include (1) a history or suspicion of ethylene glycol ingestion, (2) an elevated anion-gap acidosis, (3) an unexplained

serum osmolality >10 mOsm/L above the calculated serum osmolarity, (4) oxalate crystals in urine, (5) elevated ethylene glycol levels, and (6) other factors. Antidotal therapy is based on preventing the alcohol dehydrogenase enzyme from metabolizing ethylene glycol into toxic byproducts.

Ethanol will competitively inhibit alcohol dehydrogenase but the serum ethanol level must be monitored frequently. Also, therapeutic ethanol infusions can cause hypoglycemia in children and may exacerbate CNS depression. Therapeutic ethanol is administered in a bolus followed by a continuous infusion. Initially, 7.5 to 10 mL/Kg of 10% ethanol, in D5W, is administered over 30 minutes. Then, a continuous infusion of 1 to 2 mL/Kg/hr of 10% ethanol is infused until the patient has eliminated all of the EG from his serum. It is important to keep the serum ethanol level at 100 to 150 mg/dL so as to completely inhibit the alcohol dehydrogenase enzyme.

Fomepizole (Antizole) also blocks alcohol dehydrogenase, has few side effects, and is considered the drug of choice for antidotal therapy for ethylene glycol or methanol toxicity. Fomepizole is administered as follows: 15 mg/Kg (up to 1 Gm) initially, then 10 mg/Kg q12h times four doses, and then 15 mg/Kg q12 hours until EG level <10 mg/dL.

In patients who are symptomatic, hemodialysis should be considered. Hemodialysis efficiently clears ethylene glycol and toxic byproducts and corrects acidosis. If the patient does receive dialysis, treatment with fomepizole and ethanol should continue to be provided so as to block the ongoing conversion of EG to its toxic metabolites while dialysis is being performed. Both fomepizole and ethanol will be dialyzed off and their dosing needs to be adjusted accordingly.

Use of sodium bicarbonate enhances elimination of toxic byproduct by correction of acidosis.

Pyridoxine (50mg q6 hours) may inhibit metabolism of glycolic acid to oxalic acid by acting as cofactor in metabolism of glycolic acid to nonoxalate byproducts. Thiamine (100mg q6 hours; 50mg q6 hours in children) is recommended to stimulate the conversion of glyoxylate to alpha-hydroxy-beta-ketoadipate, a non-toxic metabolite

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