PRODUCT MONOGRAPH

ANTIZOL®
(fomepizole) Injection

ORPHAN MEDICAL

DEDICATED TO PATIENTS WITH UNCOMMON DISEASES®

Ethylene glycol and methanol poisoning represent potentially life-threatening emergencies and each situation involves unique circumstances. This monograph is designed to give an appreciation for the complexity of these critical situations and their requirement for antidotal treatment, but is not a comprehensive manual for treatment. In the event of a confirmed or suspected ethylene glycol or methanol poisoning, the clinician is encouraged to contact Orphan Medical (24 hours per day) or a regional poison control center for treatment recommendations and consultation with a medical toxicologist.

For questions of a medical nature, call
1-888-8ORPHAN (1-888-867-7426).

Overview

Ethylene glycol poisoning is considered a medical emergency. Despite being recognized as a poison for nearly 50 years, ethylene glycol remains readily available and continues to be fatally ingested. The most common sources of ethylene glycol are automotive antifreeze (generally available as a 95% concentration), engine coolants and hydraulic brake fluids.

In ethylene glycol poisoning, the clinical course is initially characterized by mild symptoms that may gradually develop to produce serious or even fatal toxicity. Ethylene glycol poisoning presents many challenges in making a definitive diagnosis. If treatment is initiated early, prognosis is excellent. However, a disturbing proportion of patients are admitted at a late stage to hospitals that are not capable of performing analysis which identifies ethylene glycol toxicity on a 24-hour basis. Therefore, rapid treatment is often prevented because of a delayed diagnosis, which may result in fatal consequences (Jacobsen 1986).

The lethal dose of ethylene glycol is usually 1.4-1.6 mL/kg (about 100 mL in an adult), but as little as 30 mL may be fatal (Walder 1994).

Occurrence

Ethylene glycol poisoning occurs infrequently, either intentionally through abuse or attempted suicide, or unintentionally through misuse or accident (environmental or occupational).

There is a lack of comprehensive data available on the incidence of ethylene glycol poisoning in the United States. However, the American Association of Poison Control Centers (AAPCC) publishes an annual report of Toxic Exposure Surveillance System (TESS) data. This report is a compilation of human toxic exposure cases reported to the AAPCC by the majority of U.S. poison centers.

In 1999, the AAPCC reported more than 2.2 million human poison exposures. Of these, 6,281 represented exposures to ethylene glycol. There were 25 reported deaths from ethylene glycol: 22 were intentional, 19 were suicides (Litovitz 2000).

Chemistry

Ethylene glycol, also known as 1,2-ethanediol or glycol alcohol, is a dihydroxy alcohol derivative of the aliphatic hydrocarbons. Ethylene glycol has a molecular formula of $C_2H_6O_2$ and a molecular weight of 62.07 grams/mole. It is a colorless, odorless, slightly viscous and considerably hygroscopic liquid (Budavari 1989A).

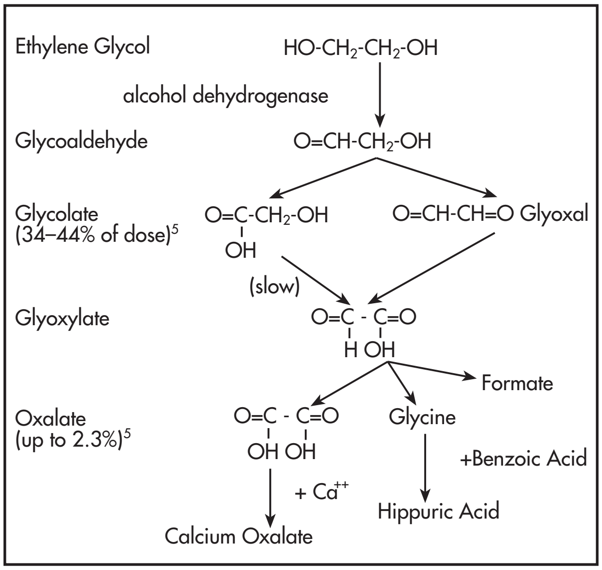
Pharmacokinetics

Ethylene glycol is rapidly absorbed from the gastrointestinal tract, reaching peak blood concentrations one to four hours after ingestion. The volume of distribution has been reported to range from 0.5-0.8 L/kg (Barceloux 1999). Primary metabolism takes place in the liver. Approximately 80% of ethylene glycol is metabolized hepatically, with 20% being excreted unchanged. The elimination half-life of ethylene glycol is approximately three hours, but is prolonged to 17-18 hours following inhibition of alcohol dehydrogenase (Barceloux 1999).

Mechanism of Toxicity

Knowledge of the metabolism of ethylene glycol is critical to the understanding of the pathogenesis of its toxicity and the rationale behind therapy. While the parent compound is essentially nontoxic, ethylene glycol metabolites are responsible for extensive cellular damage in various tissues, especially the kidneys, caused principally by the metabolites glycolate and oxalate (or glycolic and oxalic acid, depending upon the serum pH).

Figure 1. Metabolic Pathway of Ethylene Glycol Toxicity (Adapted from Walder 1994)



The metabolism of ethylene glycol is a four-step process, taking place primarily in the liver. (See Figure 1.) During the first step, ethylene glycol is metabolized to glycoaldehyde via alcohol dehydrogenase (ADH). Glycoaldehyde is then rapidly converted to glycolate via aldehyde dehydrogenase in the second step. The third step is the further metabolism from glycolate to glyoxylate, which occurs relatively slowly, allowing for accumulation of glycolate. The production of glycolate interferes with cellular metabolic enzymes and is also responsible for the severe metabolic acidosis characteristic of poisoning by ethylene glycol. The small amounts of lactate and formate produced are clinically insignificant. Glyoxylate and formate, although more toxic than glycolate on a weight-for-weight basis, are only formed in micromolar amounts and do not contribute to toxicity. The fourth step is the metabolism of glyoxylate to produce oxalate, which rapidly precipitates as calcium oxalate and is deposited in a crystalline form, especially the kidneys (Walder 1994).

Clinical Course

Many authors describe three stages of ethylene glycol poisoning: a neurological stage, followed by a cardiopulmonary stage, and finally, a renal stage. In many cases, however, there is considerable overlap among the three phases. One may predominate while another may be absent and they may occur at different times than described here (Barceloux 1999).

Stage 1: Neurological (30 minutes to 12 hours after ingestion)

The early neurological effects follow a biphasic course. Within minutes to several hours after ethylene glycol poisoning, transient inebriation and euphoria, similar to the symptoms of ethanol intoxication, may be observed. Nausea and vomiting can also occur. As ethylene glycol metabolism progresses, metabolic acidosis and central nervous system (CNS) depression can replace earlier symptoms. About 4-12 hours after ingestion, symptoms associated with toxic metabolites of ethylene glycol predominate. However, their onset can be delayed if a patient has also ingested substantial amounts of ethanol, which inhibits ethylene glycol metabolism. In severe cases, these symptoms can include coma associated with hypotonia, hyporeflexia, occasional seizures and meningismus. Cytotoxicity and the deposition of calcium oxalate can lead to cerebral damage and contribute to CNS depression. Other neurological symptoms may include nystagmus, ataxia, opthalmoplegias and myoclonic jerks. In most cases of ethylene glycol poisoning, the optic fundus is normal. However, in some situations, the presence of papilledema may confuse the clinical presentation with that of methanol poisoning (Barceloux 1999).

Stage 2: Cardiopulmonary (12-24 hours after ingestion)

In the second stage of ethylene glycol poisoning, tachycardia and mild hypertension frequently occur. In serious cases, severe metabolic acidosis with compensatory hyperventilation can develop accompanied by multiple organ failure. Most deaths occur in this stage (Barceloux 1999).

Stage 3: Renal (24-72 hours after ingestion)

The symptoms of the third stage can include oliguria, flank pain, acute tubular necrosis, renal failure and, in rare instances, bone marrow suppression. In severe cases of ethylene glycol poisoning, renal failure may appear early and progress to anuria. Recovery of renal function is often complete but may require several months of hemodialysis. Even when renal damage is severe, chronic hemodialysis or renal transplantation are rarely required. Serious damage to the liver is rare (Barceloux 1999).

Diagnosis

Many of the clinical signs and symptoms associated with ethylene glycol and methanol poisonings (i.e. nausea, vomiting, CNS depression) are nondescript, and are similar to the clinical signs and symptoms for many poisonings and illnesses. However, there are a few key features that should immediately lead the physician to consider ethylene glycol poisoning. In a thorough patient history, there should be a distinct period of latency between consumption and the appearance of toxic symptoms. Respiratory distress with hyperventilation would suggest metabolic acidosis and is present in most cases. Metabolic acidosis can be rapidly determined by electrolyte or arterial blood gas analysis. Increases in the anion and osmolal gap also point to this poisoning. Ethylene glycol poisoning must always be considered in any patient presenting with metabolic acidosis of unknown origin.

Rapid diagnosis of ethylene glycol toxicity is critical because therapy can be very effective when applied within a reasonable period of time after ingestion. Conversely, in many cases when diagnosis is delayed, antidotal therapy is of little use, often with fatal consequences (Jacobsen 1986).

The key to rapid diagnosis is to obtain a thorough history from the patient, a friend, or family member. This can be challenging in some cases because patients are often confused, distressed or even comatose. The time delay between consumption and patient presentation to a health care facility may hinder communication with friends or family (Jacobsen 1997).

The most conclusive method of diagnosing this poisoning is direct measurement of serum or urine ethylene glycol concentration. However, patients are sometimes admitted at a late stage to hospitals that are not capable of performing analysis of this compound on a 24-hour basis. Because this compound becomes toxic after conversion to its metabolites, there is little correlation between blood concentrations of the ethylene glycol, per se, and the severity of the poisoning. In many cases, poisoned patients do not seek treatment until the syndrome is well developed, when blood ethylene glycol concentrations are low, but toxic metabolite concentrations are high. Other patients present asymptomatically during the latent period following ingestion (Jacobsen 1997).

In situations where specific analyses are not available, the calculation of the anion and osmolal gaps can provide relatively certain and early diagnosis, allowing treatment to be started immediately. Calculation of the anion and osmolal gaps should be performed by the clinician whenever facing a metabolic acidosis of unknown origin (Jacobsen 1997). The anion gap may be calculated as follows:

Anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$,
where normal = 12-16 mmol/L

or by convention:

Anion gap = $(Na^+) - (Cl^- + HCO_3^-)$,
where normal = 8-12 mmol/L.

A metabolic acidosis with an increased anion gap and a normal chloride concentration indicates retention of nonvolatile organic acids, such as may be present in renal failure, ketoacidosis, lactic acidosis, and ingestion of substances such as methanol, ethylene glycol, salicylate or iron. In the absence of circulatory failure, diabetes, alcoholism and uremia, an increased anion gap clearly indicates poisoning with one or more of these substances (Jacobsen 1997).

The diagnostic importance of the anion gap increases if combined with consideration of the osmolal gap (Jacobsen 1986). The osmolal gap is the difference between the measured osmolality and the calculated osmolality in serum. Normally, sodium, glucose and urea (BUN) principally determine the osmolality of serum as expressed by the formula:

Osmolal gap (mOsm/kg) = (1.86 x Na^+ [mEq/L]) + (BUN [mg/dL]/2.8) + (glucose [mg/dL]/18)
where normal = 270-290 mOsm/kg

or

SI units (mmol/kg) = (1.86 x Na^+ [mmol/L] + BUN [mmol/L] + glucose [mmol/L])/0.93
where normal = 280-300 mmol/kg.

An increased osmolal gap indicates that one or more intoxicants are present in high molar concentrations. Most drugs, including salicylates, are not identified this way because they are dissociated or do not attain high enough serum concentration on a molar basis. The intoxicants best able to increase the osmolal gap are those that have a low molecular weight and are present in high mass units. The lower alcohols and glycols are such substances. Methanol and ethylene glycol regularly cause severe metabolic acidosis and elevation of both the anion and osmolal gaps (Jacobsen 1997).

The osmolal gap should be cautiously interpreted in the critically ill patient, because any circulatory failure may increase its value. Parenteral infusions with hyperosmolar solutions and the presence of diabetic ketoacidosis may also expand the osmolar gap. Chronic renal failure also contributes to a slight elevation, while acute renal failure leaves it unaltered (Jacobsen 1986).

Serum osmolality must be performed with the freezing point depression method; the vapor pressure method is not valid and should not be used. If ethanol is co-ingested with ethylene glycol, there may be no metabolic acidosis until most of the ethanol is metabolized due to the competitive ADH-inhibiting effect of ethanol. In such circumstances, calculation of the gaps must be repeated. In late stages of a poisoning, most of the ethylene glycol may be metabolized to its acidic metabolites. In this situation, there may be a pronounced metabolic acidosis with a high anion gap but the osmolal gap may be close to normal values. Under these conditions, a small/normal osmolal gap does not eliminate the possibility of toxic alcohol ingestion (Jacobsen 1997).

Urinary calcium oxalate crystals are present on admission in almost 50% of ethylene glycol-poisoned patients and this percentage increases if urine microscopy is repeated later in the course of the intoxication. X-ray diffraction studies in humans have shown that the needle-shaped monohydrate crystals (Whewellite) are more common than the envelope-shaped dihydrate crystals (Weddelite). The dihydrate is meta-stable and will undergo transformation to the monohydrate form. The crystalluria may be massive and generally accompanied by some red cells and different types of casts. If specific analyses are not available, repeated urine microscopy is very useful in the differential diagnosis in patients presenting with metabolic acidosis of unknown origin (Jacobsen 1997).

Treatment Objectives

Rapid diagnosis of ethylene glycol toxicity is critical because therapy can be very effective when applied within a reasonable period of time after ingestion. Conversely, in many cases when diagnosis is delayed, antidotal therapy may be of little use, often with fatal consequences. The metabolic products of ethylene glycol can produce acidosis; when considerable time has elapsed after ingestion, mortality correlates best with the severity of acidosis rather than blood ethylene glycol concentration. Therefore, both ethylene glycol concentrations and acid base balance, as determined by electrolyte (anion gap) and/or arterial blood gas analysis, should be frequently monitored and used to guide treatment.

Treatment of ethylene glycol poisoning involves three primary goals: correction of the patient's metabolic acidosis, prevention of metabolism of the compound to its toxic metabolites, and removal of ethylene glycol and its toxic metabolites with hemodialysis, if necessary.

Gastric lavage may be indicated if performed soon after ingestion, or in patients who are comatose or at risk for convulsions. Ipecac is considered contraindicated because of the potential for CNS depression from the ethylene glycol and the potential for convulsions (Barceloux 1999). Charcoal is of little benefit as ethylene glycol is not significantly absorbed by activated charcoal; in cases of multiple chemical ingestions, however, it would be used for the co-ingestant(s) (Jacobsen 1997).

Because of the potential for CNS depression, airway protection may be indicated and respiratory support provided as needed. Intravenous (IV) fluids may be needed to correct electrolyte imbalance and to maintain adequate urine output. Urine output needs to be carefully monitored. However, if renal failure develops, IV fluids may need to be withdrawn to avoid fluid overload. Pyridoxine and thiamine may be administered to patients with ethylene glycol poisoning to promote alternate metabolism or conversion to non-toxic metabolites glycine and ∝-hydroxy-ß-ketoadipate. However, data supporting a beneficial effect of pyridoxine and thiamine is sparse.

Calcium should not be given for hypocalcemia, per se, as this may increase precipitation of calcium oxalate crystals in the tissues (Jacobsen 1997). However, in ethylene glycol poisoned patients, tetany and seizures may require treatment with IV calcium gluconate/chloride, as hypocalcemia is an important cause of these complications.

Early and aggressive treatment with sodium bicarbonate is generally considered essential, to correct the initial acidosis. With the emphasis on antidotal therapy, physicians must not forget the importance of alkali therapy. More than 500-1000 mmol bicarbonate may be needed within the first hours, especially if antidotal therapy has not been initiated. In ethylene glycol poisoning, clinical experience has shown that hypocalcemia may be worsened during aggressive alkali therapy because alkalinization increases the protein binding of calcium (Jacobsen 1997).

The dialysance of ethylene glycol and its major metabolite glycolate has been well established. According to the traditional toxicology literature, hemodialysis should be considered in cases with a serum ethylene glycol concentration greater than 50 mg/dL (Barceloux 1999).

Unfortunately, hemodialysis is not available in all hospitals. In the event of a serious poisoning where extracorporeal removal of ethylene glycol may be indicated, transferring the patient to a facility with renal dialysis capabilities should be considered.

Peritoneal dialysis also removes ethylene glycol and its metabolites, although not as effectively as hemodialysis. Hemoperfusion is ineffective (Jacobsen 1997).

Prognosis

Outcomes are excellent for ethylene glycol poisoned patients, provided there is early treatment with alkali to combat acidosis, antidotal therapy and hemodialysis, if necessary, to remove the ethylene glycol and its toxic metabolites (Jacobsen 1986).

Overview

Methanol is a highly toxic alcohol commonly found in automobile windshield washer solvent, gas line antifreeze, copy machine fluid, fuel for small stoves, paint strippers and as an industrial solvent (Budavari 1996B; Suit 1990). Many new uses for methanol, predominantly as an alternative energy source, have also been proposed. If these new applications are developed, methanol is likely to become even more accessible in the future and therefore, more available for misuse.

As with ethylene glycol, the clinical course of methanol poisoning develops over a number of hours. While methanol itself is only mildly intoxicating, it is converted to highly toxic metabolites responsible for acidosis, blindness and potentially death. Because the morbidity of methanol poisoning is related to delay in treatment, real or suspected methanol poisoning must be aggressively treated. Methanol poisoning creates many challenges for clinicians because laboratory tests, antidotes and intensive care facilities are not always available.

The lethal dose of pure methanol is estimated to be 1-2 mL/kg (Jacobsen 1986). However, permanent blindness and death have been reported with as little as 0.1 mL/kg (6-10 mL in adults) (ATSDR 1993).

Occurrence

In the 1999 Annual Report of the Toxic Exposure Surveillance System by the American Association of Poison Control Centers, more than 2.2 million human poison exposures were reported. Of these, 2,417 represented exposures to methanol. There were 11 deaths attributed to methanol and, in all cases, these ingestions were intentional in nature. Seven cases represented suicides, two were cases of abuse, while the actual intent was unknown among the remaining fatalities (Litovitz 2000).

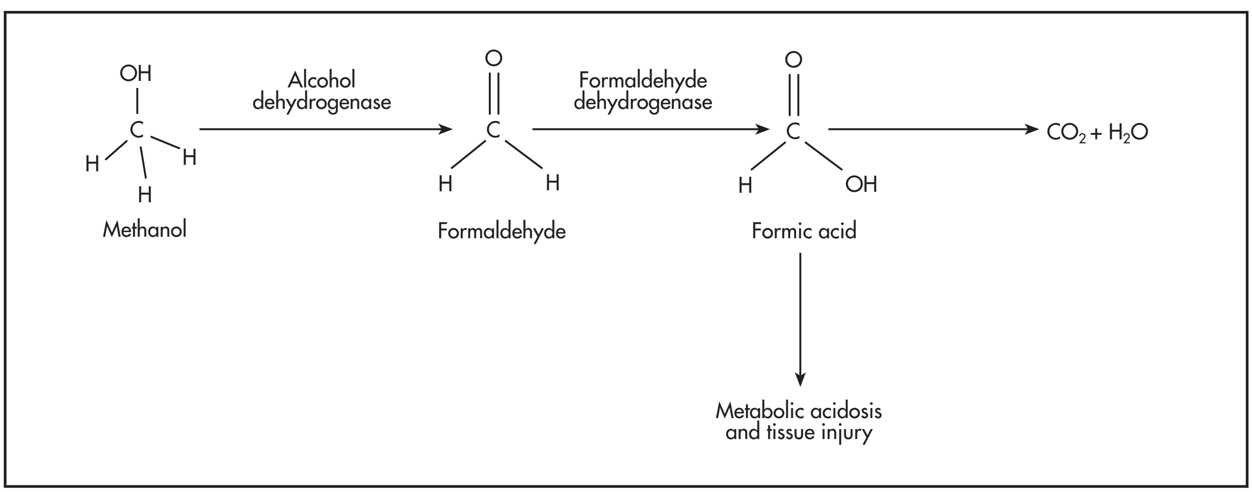
Chemistry

Methanol, also known as methyl alcohol and wood alcohol, is a primary alcohol with the chemical formula CH_3OH, a molecular weight of 32.04, a specific gravity of 0.81 and a boiling point of 65°C. It is colorless, volatile, flammable and readily miscible in water (Budavari 1996B). It also has a slight odor that is distinctly different from that of ethanol.

Pharmacokinetics

Methanol is readily absorbed from the gut, skin and lungs. Peak serum concentration usually occurs in 30-60 minutes following ingestion. Methanol distributes widely in body water with a volume of distribution of 0.6 L/kg. Methanol is slowly and erratically metabolized in the liver and follows zero order kinetics. Approximately 3% of a methanol dose is excreted through the lungs or excreted unchanged in the urine. The half-life of methanol is prolonged to 30-50 hours during antidotal therapy (Palatnick 1995).

Figure 2. Metabolic Pathway of Methanol Toxicity (Adapted from Brent 2001)



Mechanism of Toxicity

Like ethylene glycol, methanol is relatively non-toxic. However, it is metabolized to highly toxic compounds that are responsible for the acidosis and blindness characteristic of methanol poisoning.

As in ethylene glycol poisonings, the initial step in the metabolism of methanol involves the enzyme alcohol dehydrogenase (ADH). (See Figure 2.) First, methanol is slowly oxidized by ADH to yield formaldehyde. Next, formaldehyde is oxidized by formaldehyde dehydrogenase to yield formic acid (or formate, depending on the pH). This oxidation occurs rapidly so that little formaldehyde accumulates in the serum. Finally, formic acid is metabolized to carbon dioxide and water, which are excreted by the kidneys and lungs.

The accumulation of formic acid is partly responsible for the presence of metabolic acidosis. Formic acid also inhibits cellular respiration leading to lactic acidosis. The ocular injury caused by methanol may be due to retinal injury, which results from intra-retinal metabolism of methanol and the accumulation of formic acid. Alternatively, it may be caused by the inhibition of normal metabolism in optic nerve cells (Jacobsen 1997).

Clinical Course

Initial symptoms of methanol poisoning may appear as soon as 12 hours post-ingestion, but usually develop 24 hours after ingestion. These may resemble ethanol intoxication and consist of drowsiness, confusion and ataxia, as well as weakness, headache, nausea, vomiting and abdominal pain. Collectively, these symptoms may mimic an alcohol hangover and are due to mild intoxication, caused by methanol itself.

As methanol metabolism proceeds, a severe anion gap metabolic acidosis will develop. Severe metabolic acidosis in conjunction with visual effects are the hallmark of methanol poisoning. Patients usually describe blurred or misty vision, double vision or changes in color perception. There may be constricted visual field and, occasionally, total loss of vision. Characteristic visual dysfunctions include pupillary dilation and loss of pupillary reflex (Burkhart 1990; Suit 1990).

Further signs and symptoms may be shallow respiration, cyanosis, tachypnea, coma, seizures, electrolyte disturbances and various hemodynamic changes including profound hypotension and cardiac arrest. There may be mild to profound loss of memory, confusion and agitation, which may progress to stupor and coma as the severity of the acidosis increases (Suit 1990). In severe cases, death is possible. Surviving patients can be left with permanent blindness or with neurological deficits (Jacobsen 1997).

Diagnosis

Methanol poisonings can be relatively difficult to diagnose when a specific history of ingestion is not available. Diagnosis requires both clinical and laboratory data, however, there may be an initial lack of clinical data for patients who are unable, or unwilling, to supply a history of ingestion. In such situations, obtaining a patient's history from family or friends can be valuable. In addition, it is often difficult for a clinician to distinguish between poisoning by methanol or by ethylene glycol.

The most direct means of diagnosing methanol poisoning is through the measurement of serum methanol concentration. The decision to perform a serum methanol determination may be based on patient disclosure of methanol ingestion or the presence of a methanol-containing product at the scene of the ingestion. Other reasons to suspect methanol poisoning may be based on clinical signs together with laboratory findings such as anion gap metabolic acidosis and an osmolal gap. According to Kearney *et al.* (1997), only 39% of teaching hospitals were able to perform serum methanol determinations in-house.

An anion gap metabolic acidosis is not immediately seen following ingestion of methanol and may be due to other types of poisoning, including iron, salicylates and ethylene glycol or disease states such as diabetic ketoacidosis or uremia. The presence of an osmolal gap may further support the diagnosis of methanol poisoning. However, its absence does not rule it out, as the osmolal gap will diminish as methanol metabolism proceeds. Also, other toxins, including other alcohols, will produce an osmolal gap. Finally, the co-ingestion of ethanol may produce a confusing clinical picture as the toxic effects of methanol may be masked or delayed (Jacobsen 1997).

Other diagnostic clues are ophthalmic changes and may include hyperemia of the optic disc or optic disc edema, and eventually, pallor (Jacobsen 1997).

A serum methanol concentration greater than 20 mg/dL soon after ingestion generally indicates the need for antidotal therapy. However, in late-presenting patients, any concentration of methanol in the presence of systemic toxicity should be treated.

Treatment Objectives

As with ethylene glycol, the three primary goals of therapy include treatment of metabolic acidosis, inhibition of the methanol metabolism and enhanced elimination of the unmetabolized compound and existing toxic metabolites.

Gastric decontamination is unlikely to be beneficial because methanol is rapidly and completely absorbed from the gut. Ipecac-induced emesis is contraindicated due to the risk of rapid loss of consciousness. It is doubtful activated charcoal has the ability to adsorb significant amounts of methanol, however it may be useful if a co-ingestant is suspected. Gastric lavage would need to be performed soon after an ingestion to be beneficial.

Stabilization of the critical patient must be performed before other therapies can be instituted. Correcting acid/base status should be a priority because serious metabolic acidosis is common and a pH less than 7 is associated with poor prognosis. Sodium bicarbonate should be administered to correct serum pH. Fluid and electrolyte replacement, airway management and the treatment of serious cardiovascular and neurological signs, such as hypotension and seizures, should also be a primary concern.

The elimination of methanol may be enhanced by administering folic acid, a cofactor in the conversion of formic acid to carbon dioxide, and by performing hemodialysis (Jacobsen 1997).

Prognosis

Outcomes are excellent when asymptomatic methanol-poisoned patients are treated promptly. Reversal of presenting blindness, in one reported case, was attributed to prompt treatment (Sivilotti 1998). According to one study, poor outcomes were associated with coma or seizures on presentation or acidosis with pH less than 7 (Liu 1997).

Ethanol has been a primary component of the therapeutic regimen for ethylene glycol and methanol poisonings since the 1960s. Ethanol therapy has been used because alcohol dehydrogenase has a much greater affinity for ethanol than for ethylene glycol or methanol, and a sufficiently high concentration of ethanol inhibits the production of the toxic metabolites. Historically, if ethylene glycol or methanol concentrations were greater than 20 mg/dL, ethanol therapy would be initiated.

There are, however, many challenges involved in ethanol administration. The first challenge can be obtaining the product. Ethanol can be dosed either orally or intravenously. If dosed orally, the patient can be given beverage alcohol, such as gin or vodka. However, such alcohols are not usually stocked in hospital pharmacies and obtaining them can consume valuable time. Similarly, the intravenous form of ethanol may not be stocked and must be compounded in the pharmacy, taking valuable time and delaying treatment.

The next challenge involves managing the ethanol therapy and the ethanol-treated patient. Therapeutic ethanol blood concentrations are difficult to maintain because of ethanol's rapid and erratic metabolism. If the ethanol concentration is too high, it compounds the effects of the underlying poisoning, since ethanol is both a CNS depressant and a hepatotoxin. If it is too low, it may not effectively inhibit metabolism. Because the rate of ethanol metabolism depends on the patient's history of alcohol use, serum alcohol concentration must be monitored repeatedly and the rate of administration adjusted accordingly. Also, because ethanol is readily dialyzable, further adjustments must be made during hemodialysis. Consequently, ethanol blood concentrations must be monitored at least once every 1-2 hours for the first 8-12 hours of treatment and frequently thereafter. The presumed therapeutic ethanol concentrations are considered to be 100-125 mg/dL and patients typically remain in this intoxicated state for several days. During this time, patients may need to be intubated and sedated, depending upon their condition at presentation. Adverse reactions to ethanol therapy include CNS depression that may exacerbate poisoning symptoms, agitation, hepatoxicity and hypoglycemia, especially in children.

Patients may often require observation in a hospital intensive care unit for an additional 24 hours in order to recover from excessive ethanol blood concentrations.

Overall, "though ethanol is an effective and available antimetabolite for these intoxications, its use is labor intensive and hampered by dosage problems, a relatively rapid elimination (especially during hemodialysis), and side effects like significant CNS depression in these often critically ill patients" (Jacobsen 1996).

Introduction

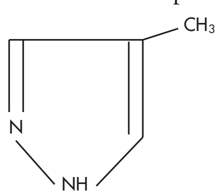
Fomepizole, commonly referred to as 4-methylpyrazole or 4-MP, is a relatively recent addition to the therapeutic regimens for ethylene glycol and methanol poisonings. Fomepizole, as either the sulfate or hydrochloride salt, has been available in France since 1981 through a centralized compounding pharmacy servicing French hospitals. Until about 1990, fomepizole was used there investigationally to treat ethylene glycol poisonings. Since 1990, fomepizole has been accepted as the standard of care in France for the treatment of ethylene glycol poisonings.

In 1997, Antizol® (fomepizole) Injection was approved by the FDA as an antidote for ethylene glycol (antifreeze) poisoning or for use in suspected ethylene glycol ingestion. It was also approved in the United Kingdom during 1999 and in Canada during 2000 for use in ethylene glycol poisoning. In 2000, Antizol was approved by the FDA for an additional indication as an antidote for methanol poisoning or for use in suspected methanol ingestion.

Chemistry

Figure 3. Chemical Structure of Antizol

Antizol is the free base form of fomepizole, which has



a molecular formula of $C_4H_6N_2$ and a molecular weight of 82.1 grams/mole. Antizol is a clear, colorless to yellow liquid at room temperature, but may solidify below 25°C (77°F). Solidification does not affect the efficacy, safety or stability of Antizol [Antizol® (fomepizole) Injection package insert]. Its chemical structure is shown in Figure 3.

Mechanism of Action

Antizol is a competitive inhibitor of alcohol dehydrogenase, the enzyme that catalyzes the oxidation of ethanol to acetaldehyde. Alcohol dehydrogenase also catalyzes the initial steps in the metabolism of ethylene glycol and methanol to their toxic metabolites.

Absorption, Bioavailability and Distribution

Intended for administration by the intravenous route, Antizol is immediately and completely bioavailable. Antizol rapidly distributes to total body water. The volume of distribution is between 0.6 L/kg and 1.02 L/kg [Antizol® (fomepizole) Injection package insert].

Metabolism and Excretion

In healthy volunteers, only 1-3.5% of an administered dose of Antizol (7-20 mg/kg oral and IV) was excreted unchanged in the urine, indicating that metabolism is the major route of elimination (Jacobsen 1990). In humans, the primary metabolite of Antizol is 4-carboxypyrazole (4-CP), which is excreted in the urine.

Other minor metabolites of fomepizole observed in the urine are 4-hydroxymethylpyrazole and the N-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole. These metabolites are either inactive or are so weak (4-hydroxymethylpyrazole) that they do not contribute significantly to the inhibition of alcohol dehydrogenase (Weintraub 1988).

The elimination of Antizol is enhanced after several doses at 12-hour intervals, suggesting that it induces its own metabolism. Following auto-induction, a first order kinetic model more closely describes the elimination of Antizol. The metabolism of Antizol to 4-CP occurs after an initial cytochrome P-450-mediated hydroxylation followed by further oxidation. As Antizol is a potent inducer of cytochrome P-450-mediated drug elimination in animal studies, the auto-induction of Antizol elimination in humans over 36-48 hours may also involve the induction of cytochrome P-450 (Jacobsen 1990).

The elimination of Antizol follows zero order, saturable Michaelis-Menten kinetics after acute doses and a first order kinetic model after induction of metabolism following chronic doses. Values for plasma half-life vary with dose and were therefore not calculated in early study reports.

The efficacy of Antizol® (fomepizole) Injection as an antidote for both ethylene glycol and methanol toxicity has been clearly documented. Some of the publications are briefly summarized here.

Ethylene Glycol

Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. *Clinical Toxicology* 1999; 37(5): 537-560.

This paper is an extensive review of all aspects of ethylene glycol poisoning and its treatment. Suggested indications for use of an antidote are: documented plasma ethylene glycol concentration greater than 20 mg/dL OR documented recent ingestion of toxic quantity of ethylene glycol and an osmol gap greater than 10 mosm/L OR a strong suspicion of ethylene glycol poisoning AND at least two of the following criteria: arterial pH less than 7.3; serum bicarbonate less than 20 mEq/L; an osmol gap greater than 10 mosm/L; or the presence of urinary oxalate crystals. Fomepizole is indicated for the treatment of ethylene glycol poisoning unless unavailable or the patient has a hypersensitivity to fomepizole.

Brent J, McMartin K, Philips S, Burkhart KK, Donovan JW, Wells M, Kulig K. Fomepizole for the Treatment of Ethylene Glycol Poisoning. *New England Journal of Medicine* 1999; 340:832-838.

This prospective, multicenter clinical trial evaluated the use of fomepizole in 19 cases of ethylene glycol poisoning. In each case, the serum ethylene glycol concentration was greater than 20 mg/dL. Seventeen patients underwent hemodialysis in addition to receiving fomepizole. Nine patients suffered decreased renal function; all nine had elevated plasma creatinine and glycolate concentrations on presentation. The remaining patients experienced no evidence of subsequent renal injury. The authors concluded that administration of fomepizole early in the course of ethylene glycol poisoning inhibits the formation of toxic metabolites and thereby prevents renal injury.

Borron SW, Mégarbane B, Baud FJ. Fomepizole in Treatment of Uncomplicated Ethylene Glycol Poisoning. *Lancet* 1999; 354:831.

This group treated 38 patients for clinical suspicion of ethylene glycol poisoning. Eleven subsequently were found to have serum ethylene glycol concentrations of 20 mg/dL or more. Three of these patients were dialyzed because of renal insufficiency and acidosis and one because serum ethylene glycol concentration was 831 mg/dL. One patient who presented with multiorgan failure died. Seven patients who presented with normal renal function and treated with fomepizole alone experienced no evidence of subsequent renal injury. The authors suggested that, in the absence of renal insufficiency and acidosis, fomepizole alone may be sufficient to treat patients poisoned with ethylene glycol.

Sivilotti MLA, Burns MJ, McMartin KE, Brent J. Toxicokinetics of Ethylene Glycol During Fomepizole Therapy: Implications for Management. *Annals of Emergency Medicine* 2000; 36:114-125.

The kinetics of ethylene glycol elimination were studied in ethylene glycol-poisoned patients treated with fomepizole. The elimination half-life was significantly longer in fomepizole-treated patients, indicating hepatic metabolism was inhibited. Without hepatic metabolism, the rate of renal ethylene glycol excretion was directly proportional to creatinine clearance. Patients with normal creatinine clearance were able to excrete ethylene glycol more rapidly than those with elevated creatinine and presumed renal injury. The authors concluded that serum creatinine in ethylene glycol-poisoned patients at time of presentation can be used to determine which patients will require hemodialysis. In patients treated with fomepizole, a serum ethylene glycol concentration of 50 mg/dL or greater should no longer be used as sole criteria for hemodialysis.

Methanol

Brent J, McMartin K, Phillips S, Aaron C, Kulig K. Fomepizole for the Treatment of Methanol Poisoning. *New England Journal of Medicine* 2001; 344:424-429.

This prospective, multicenter clinical trial examined the effectiveness of fomepizole for the treatment of methanol poisoning in 11 consecutive patients with serum methanol concentrations greater than 20 mg/dL. Eight patients had measurable plasma formic acid concentrations on presentation, which were inversely related to serum pH. Seven patients had visual abnormalities. Following initiation of fomepizole treatment, formic acid concentrations fell with simultaneous improvement in plasma pH, visual disturbances and other symptoms related to the ingestion. Seven patients also underwent hemodialysis. The authors suggested that hemodialysis may not be necessary in cases where patients are not acidotic and are receiving fomepizole, but may be warranted in patients with high serum methanol concentrations to prevent lengthy hospital stays. The investigators concluded fomepizole is safe and effective in the treatment of methanol poisoning.

Baud F, Borron S. An Open-label Study for Patients Treated with Fomepizole for Methanol Poisoning in France (unpublished).

In this French trial, five patients were evaluated for acute methanol poisoning. On presentation, plasma methanol concentrations ranged from 10-425.6 mg/dL. The patient with the highest methanol concentration presented 12-24 hours post-ingestion with a pH of 7.26. He was treated with fomepizole as well as hemodialysis but, because of the severity of the intoxication and the length of time which elapsed prior to seeking help, the patient suffered bilateral blindness. The remaining patients presented with normal pH, received fomepizole therapy only and survived without sequellae. These investigators concluded that fomepizole is a safe and effective antidote for the treatment of methanol poisoning.

Introduction

The few adverse effects observed with Antizol® (fomepizole) Injection administration have been brief and of mild to moderate severity. Possible laboratory abnormalities have been transient and have not produced clinical manifestations. Therefore, treatment with Antizol is considered safe when administered at recommended doses.

Adverse Reactions

The adverse reactions listed below are a compilation of effects reported during clinical trials where investigators indicated the effects were possibly, probably or definitely related to Antizol, or the relationship to Antizol was considered unknown. In addition, these adverse reactions include those reported by healthy volunteers who received doses that were 6-10 times greater than the recommended dose (Jacobsen 1988). Due to the clinical manifestations of ethylene glycol and methanol poisonings, it is difficult to determine whether each of the reported adverse events is due to the drug or to toxicosis.

The most frequent adverse events reported in the 78 patients and 63 normal volunteers who received Antizol were headache (14%), nausea (11%) and dizziness, increased drowsiness and bad taste/metallic taste (6% each). All other adverse events reported in approximately 3% or fewer of those receiving Antizol were as follows:

Body as a Whole:
Abdominal pain, fever, multiorgan system failure, pain during Antizol injection, inflammation at injection site, lumbalgia/backache, hangover.

Cardiovascular:
Sinus bradycardia/bradycardia, phlebosclerosis, tachycardia, phlebitis, shock, hypotension.

Gastrointestinal:
Vomiting, diarrhea, dyspepsia, heartburn, decreased appetite, transient transaminitis.

Hemic/Lymphatic:
Eosinophilia/hypereosinophilia, lymphangitis, disseminated intravascular coagulation, anemia.

Nervous:
Lightheadedness, seizure, agitation, feeling drunk, facial flush, vertigo, nystagmus, anxiety, “felt strange”, decreased environmental awareness.

Respiratory:
Hiccups, pharyngitis.

Skin/Appendages:
Application site reaction, rash.

Special Senses:
Abnormal smell, speech/visual disturbances, transient blurred vision, roar in ear.

Urogenital:
Anuria.

Laboratory abnormalities possibly related to Antizol treatment include slight transient increases in liver enzymes, eosinophilia, and elevated triglycerides and/or cholesterol. (Jacobsen 1990). These effects have not produced clinical manifestations. Significant laboratory abnormalities observed in patients, such as increased lactate, azotemia and anemia, are likely due to the toxins ingested, rather than treatment with fomepizole.

Overdosage

Nausea, dizziness and vertigo were noted in healthy volunteers receiving 50 and 100 mg/kg doses of Antizol (at plasma concentrations of 290-520 µmol/L, 23.8-42.6 mg/L). These doses are 3-6 times the recommended dose. This dose-dependent CNS effect was short-lived in most subjects and lasted up to 30 hours in one subject.

Antizol is dialyzable and hemodialysis may be useful in treating cases of overdosage.

Precautions

General:
Antizol should not be given undiluted or by bolus injection. Venous irritation and phlebosclerosis were noted in two of six normal volunteers given bolus injections (over 5 minutes) of Antizol at a concentration of 25 mg/mL.

Minor allergic reactions (mild rash, eosinophilia) have been reported in a few patients receiving

Antizol. Therefore, patients should be monitored for signs of allergic reactions.

Laboratory Tests:
In addition to specific antidote treatment with Antizol, patients intoxicated with ethylene glycol or methanol must be managed for metabolic acidosis, acute renal failure (ethylene glycol), adult respiratory distress syndrome, visual disturbances (methanol) and hypocalcemia. Fluid therapy and sodium bicarbonate administration are potential supportive therapies. In addition, potassium and calcium supplementation and oxygen administration are usually necessary. Hemodialysis is necessary in the anuric patient or in patients with severe metabolic acidosis or azotemia. Treatment success should be assessed by frequent measurements of blood gases, pH, electrolytes, BUN, creatinine and urinalysis, in addition to other laboratory tests as indicated by individual patient conditions. At frequent intervals throughout the treatment, patients poisoned with ethylene glycol should be monitored for ethylene glycol concentrations in serum and urine, and the presence of urinary oxalate crystals. Similarly, serum methanol concentrations should be monitored in patients poisoned with methanol. Electrocardiography should be performed because acidosis and electrolyte imbalances can affect the cardiovascular system. In the comatose patient, electroencephalography may also be required. In addition, hepatic enzymes and white blood cell counts should be monitored during treatment, as transient increases in serum transaminase concentrations and eosinophilia have been noted with repeated Antizol dosing.

Drug Interactions:
Oral doses of Antizol (10-20 mg/kg), via alcohol dehydrogenase inhibition, significantly reduced the rate of elimination of ethanol (by approximately 40%) given to healthy volunteers in moderate doses. Similarly, ethanol decreased the rate of elimination of Antizol (by approximately 50%) by the same mechanism.

Reciprocal interactions may occur with concomitant use of Antizol and drugs that increase or inhibit the cytochrome P450 system (e.g., phenytoin, carbamazepine, cimetidine, ketoconazole), though this has not been studied.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
There have been no long-term studies performed in animals to evaluate carcinogenic potential.

There was a positive Ames test result in the *Escherichia coli* tester strain WP2*uvr*A and the *Salmonella typhimurium* tester strain TA102 in the absence of metabolic activation. There was no evidence of a clastogenic effect in the *in vivo* mouse micronucleus assay.

In rats, fomepizole (110 mg/kg) administered orally for 40-42 days resulted in decreased testicular mass (approximately 8% reduction). This dose is approximately 0.6 times the human maximum daily exposure based on surface area (mg/m2). This reduction was similar for rats treated with either ethanol or fomepizole alone. When fomepizole was given in combination with ethanol, the decrease in testicular mass was significantly greater (approximately 30% reduction) compared to those rats treated exclusively with fomepizole or ethanol.

Pregnancy:
Pregnancy Category C: Animal reproduction studies have not been conducted with fomepizole. It is also not known whether Antizol can cause fetal harm when administered to pregnant women or can affect reproduction capacity. Antizol should be given to pregnant women only if clearly needed.

Nursing Mothers:
It is not known whether fomepizole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Antizol is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

In two case studies, pediatric patients with ethylene glycol levels greater than 20 mg/dl were treated with fomepizole and recovered without sequelae (Baum 2000, Boyer 2000).

Geriatric Use:
Safety and effectiveness in geriatric patients have not been established.

Contraindications

The only contraindication for Antizol is documented, serious hypersensitivity to fomepizole or other pyrazoles.

Indications and Usage

Antizol® (fomepizole) Injection is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning, or for use in suspected ethylene glycol or methanol ingestion, either alone or in combination with hemodialysis.

Treatment with Antizol

Begin Antizol treatment immediately upon suspicion of ethylene glycol or methanol ingestion based on patient history and/or anion gap metabolic acidosis, increased osmolar gap, visual disturbances or oxalate crystals in the urine, OR a documented serum ethylene glycol or methanol concentration greater than 20 mg/dL.

Hemodialysis

Hemodialysis should be considered in addition to Antizol in the case of renal failure, significant or worsening metabolic acidosis or a measured ethylene glycol or methanol concentration of greater than or equal to 50 mg/dL. Patients should be dialyzed to correct metabolic abnormalities and to lower the ethylene glycol concentrations below 50 mg/dL.

While hemodialysis should be considered, recent publications by the American Academy of Clinical Toxicology (AACT) and Sivilotti *et al.* suggest that ethylene glycol levels higher than 50 mg/dL may not require hemodialysis if the patient has normal renal function or is asymptomatic with a normal pH (Barceloux 1999; Sivilotti 2000).

Dosage

The treatment regimen for Antizol was designed to maintain efficacious blood concentrations throughout the course of therapy. Because no Antizol blood concentration monitoring is necessary in patients treated with this antidote, less time is required of the professional staff to maintain the treatment.

A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours thereafter until ethylene glycol or methanol concentrations are undetectable, or have been reduced below 20 mg/dL and the patient is asymptomatic with normal pH. All doses should be administered as a slow intravenous infusion over 30 minutes.

Antizol is removed by hemodialysis and the frequency of dosing should be increased during hemodialysis. The following guidelines may be used to calculate doses of Antizol in patients requiring hemodialysis. (See Table 1.)

Example 1: Patient is given a loading dose of 15 mg/kg. Hemodialysis starts 1 hour after the loading dose and lasts for 6 hours. Four hours after the start of hemodialysis, the patient would receive a dose of 10 mg/kg. Because the length of time between the last Antizol dose and the end of hemodialysis is 2 hours, the patient should receive a dose of 5 mg/kg at the end of hemodialysis. Doses of Antizol should be administered every 12 hours thereafter, until the ethylene glycol or methanol concentration is less than 20 mg/dL and the patient is asymptomatic with normal pH.

Example 2: Patient is given a loading dose of 15 mg/kg. Hemodialysis starts 7 hours after the loading dose and lasts for 45 minutes. The patient would receive a dose of 10 mg/kg prior to initiation of hemodialysis. Because the length of time between the last Antizol dose and the end of hemodialysis is less than 1 hour, the patient should receive a 10 mg/kg dose 12 hours after the dose given prior to the start of hemodialysis. Doses of Antizol should be administered every 12 hours thereafter, until the ethylene glycol or methanol concentration is less than 20 mg/dL and the patient is asymptomatic with normal pH.

Administration

Antizol solidifies at temperatures less than 25°C (77°F). If the Antizol solution has become solid in the vial, the solution should be liquefied by running the vial under warm water or by holding in the hand. Solidification does not affect the efficacy, safety or stability of Antizol. Using sterile technique, the appropriate dose of Antizol should be drawn from the vial with a syringe and injected into at least 100 mL of sterile 0.9% sodium chloride injection or dextrose 5% injection. Mix well. The entire contents of the resulting solution should be infused over 30 minutes. Antizol, like all parenteral products, should be inspected visually for particulate matter prior to administration.

Stability

Antizol diluted in 0.9% sodium chloride injection or dextrose 5% injection remains stable and sterile for at least 24 hours when stored refrigerated or at room temperature. Antizol does not contain preservatives. Therefore, maintain sterile conditions, and after dilution do not use beyond 24 hours. Solutions showing haziness, particulate matter, precipitate, discoloration, or leakage should not be used.

DOSE AT THE BEGINNING OF HEMODIALYSIS	
If <6 hours since last Antizol® dose	**If ≥6 hours since last Antizol® dose**
Do not administer dose	Administer next scheduled dose
DOSING DURING HEMODIALYSIS	
Dose every 4 hours	
DOSING AT TERMINATION OF HEMODIALYSIS	
Time between last dose and the end of hemodialysis	
<1 hour	Do not administer dose at the end of hemodialysis
1–3 hours	Administer $^{1}/_{2}$ of next scheduled dose
>3 hours	Administer next scheduled dose
DOSING FOLLOWING HEMODIALYSIS	
Give next scheduled dose 12 hours from last dose administered	

Antizol® (fomepizole) Injection inhibits alcohol dehydrogenase, the enzyme responsible for metabolizing ethanol. Therefore, Antizol is not indicated for treating ethanol poisoning, as it would prolong the period of intoxication.

Isopropyl (rubbing) alcohol is also metabolized by alcohol dehydrogenase to acetone, which is largely excreted by the kidneys and lungs (Burkhart 1990; Litovitz 1986). Because the central nervous system toxicity of isopropyl alcohol may be more dangerous than the metabolite, Antizol is not indicated in this type of poisoning.

The safety and efficacy of fomepizole to treat poisonings other that ethylene glycol and methanol poisonings have not been established.

SUMMARY

Antizol® (fomepizole) Injection provides effective and convenient intervention. Antizol may be used as soon as ethylene glycol or methanol poisoning is suspected.

- Antizol is a competitive inhibitor of alcohol dehydrogenase, the enzyme responsible for the preliminary step in the metabolism of ethylene glycol and methanol to their toxic metabolites.
- Antizol effectively blocks formation of toxic ethylene glycol metabolites, which are responsible for metabolic acidosis and renal damage.
- Antizol effectively blocks formation of toxic methanol metabolites, which are responsible for metabolic acidosis and visual disturbances.
- Simple dosing protocol based on body weight.
- Easy administration—simply dilute and infuse.
- Dialysis should be considered in some cases.

The most frequent adverse reactions to Antizol are headache (14%), nausea (11%), dizziness, increased drowsiness and bad taste/metallic taste (6% each). Ethylene glycol plasma and urine concentrations, as well as the presence of urinary oxalate crystals in ethylene glycol poisoning and methanol plasma concentrations in methanol poisoning, should be monitored throughout treatment. Minor allergic reactions (rash and eosinophilia) have been reported.

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Antizol® (fomepizole) Injection package insert.

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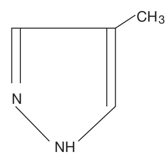
Antizol® (fomepizole) Injection
Sterile
Rx only
Caution: Must be diluted prior to use

DESCRIPTION

Antizol® (fomepizole) Injection is a competitive inhibitor of alcohol dehydrogenase.

The chemical name of fomepizole is 4-methylpyrazole. It has the molecular formula $C_4H_6N_2$ and a molecular weight of 82.1. The structural formula is:



It is a clear to yellow liquid at room temperature. Its melting point is 25° C (77° F) and it may present in a solid form at room temperature. Fomepizole is soluble in water and very soluble in ethanol, diethyl ether, and chloroform. Each vial contains 1.5 mL (1 g/mL) of fomepizole.

CLINICAL PHARMACOLOGY

Mechanism of Action

Antizol (fomepizole) is a competitive inhibitor of alcohol dehydrogenase. Alcohol dehydrogenase catalyzes the oxidation of ethanol to acetaldehyde. Alcohol dehydrogenase also catalyzes the initial steps in the metabolism of ethylene glycol and methanol to their toxic metabolites.

Ethylene glycol, the main component of most antifreezes and coolants, is metabolized to glycoaldehyde, which undergoes subsequent sequential oxidations to yield glycolate, glyoxylate, and oxalate. Glycolate and oxalate are the metabolic by-products primarily responsible for the metabolic acidosis and renal damage seen in ethylene glycol toxicosis. The lethal dose of ethylene glycol in humans is approximately 1.4 mL/kg.

Methanol, the main component of windshield wiper fluid, is slowly metabolized via alcohol dehydrogenase to formaldehyde with subsequent oxidation via formaldehyde dehydrogenase to yield formic acid. Formic acid is primarily responsible for the metabolic acidosis and visual disturbances (e.g., decreased visual acuity and potential blindness) associated with methanol poisoning. A lethal dose of methanol in humans is approximately is 1-2 mL/kg.

Fomepizole has been shown in vitro to block alcohol dehydrogenase enzyme activity in dog, monkey, and human liver. The concentration of fomepizole at which alcohol dehydrogenase is inhibited by 50% in vitro is approximately 0.1 µmol/L.

In a study of dogs given a lethal dose of ethylene glycol, three animals each were administered fomepizole, ethanol, or left untreated (control group). The three animals in the untreated group became progressively obtunded, moribund, and died. At necropsy, all three dogs had severe renal tubular damage. Fomepizole or ethanol, given 3 hours after ethylene glycol ingestion, attenuated the metabolic acidosis and prevented the renal tubular damage associated with ethylene glycol intoxication.

Several studies have demonstrated that Antizol plasma concentrations of approximately 10 µmol/L (0.82 mg/L) in monkeys are sufficient to inhibit methanol metabolism to formate, which is also mediated by alcohol dehydrogenase. Based on these results, concentrations of Antizol in humans in the range of 100 to 300 µmol/L (8.6-24.6 mg/L) have been targeted to assure adequate plasma concentrations for the effective inhibition of alcohol dehydrogenase.

In healthy volunteers, oral doses of Antizol (10-20 mg/kg) significantly reduced the rate of elimination of moderate doses of ethanol, which is also metabolized through the action of alcohol dehydrogenase (see **PRECAUTIONS, Drug Interactions**).

Pharmacokinetics

The plasma half-life of Antizol® (fomepizole) Injection varies with dose, even in patients with normal renal function, and has not been calculated.

Distribution: After intravenous infusion, Antizol rapidly distributes to total body water. The volume of distribution is between 0.6 L/kg and 1.02 L/kg.

Metabolism: In healthy volunteers, only 1-3.5% of the administered dose of Antizol (7-20 mg/kg oral and IV) was excreted unchanged in the urine, indicating that metabolism is the major route of elimination. In humans, the primary metabolite of Antizol is 4-carboxypyrazole (approximately 80-85% of administered dose), which is excreted in the urine. Other metabolites of Antizol observed in the urine are 4-hydroxymethylpyrazole and the N-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole.

Excretion: The elimination of Antizol is best characterized by Michaelis-Menten kinetics after acute doses, with saturable elimination occurring at therapeutic blood concentrations [100-300 µmol/L, 8.2-24.6 mg/L].

With multiple doses, Antizol rapidly induces its own metabolism via the cytochrome P450 mixed-function oxidase system, which produces a significant increase in the elimination rate after about 30-40 hours. After enzyme induction, elimination follows first-order kinetics.

Special Populations:

Geriatric: Antizol has not been studied sufficiently to determine whether the pharmacokinetics differ for a geriatric population.

Pediatric: Antizol has not been studied sufficiently to determine whether the pharmacokinetics differ for a pediatric population.

Gender: Antizol has not been studied sufficiently to determine whether the pharmacokinetics differ between the genders.

Renal Insufficiency: The metabolites of Antizol are excreted renally. Definitive pharmacokinetic studies have not been done to assess pharmacokinetics in patients with renal impairment.

Hepatic Insufficiency: Antizol is metabolized through the liver, but no definitive pharmacokinetic studies have been done in subjects with hepatic disease.

Clinical Studies: The efficacy of Antizol in the treatment of ethylene glycol and methanol intoxication was studied in two prospective, U.S. clinical trials without concomitant control groups. Fourteen of 16 patients in the ethylene glycol trial and 7 of 11 patients in the methanol trial underwent hemodialysis because of severe intoxication (see **DOSAGE AND ADMINISTRATION**). All patients received Antizol shortly after admission.

The results of these two studies provide evidence that Antizol blocks ethylene glycol and methanol metabolism mediated by alcohol dehydrogenase in the clinical setting. In both studies, plasma concentrations of toxic metabolites of ethylene glycol and methanol failed to rise in the initial phases of treatment. The relationship to Antizol therapy, however, was confounded by hemodialysis and significant blood ethanol concentrations in many of the patients. Nevertheless, in the post-dialysis period(s), when ethanol concentrations were insignificant and the concentrations of ethylene glycol or methanol were > 20 mg/dL, the administration of Antizol alone blocked any rise in glycolate or formate concentrations, respectively.

In a separate French trial, 5 patients presented with ethylene glycol concentrations ranging from 46.5 to 345 mg/dL, insignificant ethanol blood concentrations, and normal renal function. These patients were treated with fomepizole alone without hemodialysis, and none developed signs of renal injury.

INDICATIONS AND USAGE

Antizol is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning, or for use in suspected ethylene glycol or methanol ingestion, either alone or in combination with hemodialysis (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Antizol® (fomepizole) Injection should not be administered to patients with a documented serious hypersensitivity reaction to Antizol or other pyrazoles.

PRECAUTIONS

General:

Antizol should not be given undiluted or by bolus injection. Venous irritation and phlebosclerosis were noted in two of six normal volunteers given bolus injections (over 5 minutes) of Antizol at a concentration of 25 mg/mL.

Minor allergic reactions (mild rash, eosinophilia) have been reported in a few patients receiving Antizol (see **ADVERSE REACTIONS**). Therefore, patients should be monitored for signs of allergic reactions.

Laboratory Tests:

In addition to specific antidote treatment with Antizol, patients intoxicated with ethylene glycol or methanol must be managed for metabolic acidosis, acute renal failure (ethylene glycol), adult respiratory distress syndrome, visual disturbances (methanol), and hypocalcemia. Fluid therapy and sodium bicarbonate administration are potential supportive therapies. In addition, potassium and calcium supplementation and oxygen administration are usually necessary. Hemodialysis is necessary in the anuric patient, or in patients with severe metabolic acidosis or azotemia (see **DOSAGE AND ADMINISTRATION**). Treatment success should be assessed by frequent measurements of blood gases, pH, electrolytes, BUN, creatinine, and urinalysis, in addition to other laboratory tests as indicated by individual patient conditions. At frequent intervals throughout the treatment, patients poisoned with ethylene glycol should be monitored for ethylene glycol concentrations in serum and urine, and the presence of urinary oxalate crystals. Similarly, serum methanol concentrations should be monitored in patients poisoned with methanol. Electrocardiography should be performed because acidosis and electrolyte imbalances can affect the cardiovascular system. In the comatose patient, electroencephalography may also be required. In addition, hepatic enzymes and white blood cell counts should be monitored during treatment, as transient increases in serum transaminase concentrations and eosinophilia have been noted with repeated Antizol dosing.

Drug Interactions:

Oral doses of Antizol (10-20 mg/kg), via alcohol dehydrogenase inhibition, significantly reduced the rate of elimination of ethanol (by approximately 40%) given to healthy volunteers in moderate doses. Similarly, ethanol decreased the rate of elimination of Antizol (by approximately 50%) by the same mechanism.

Reciprocal interactions may occur with concomitant use of Antizol and drugs that increase or inhibit the cytochrome P450 system (e.g., phenytoin, carbamazepine, cimetidine, ketoconazole), though this has not been studied.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

There have been no long-term studies performed in animals to evaluate carcinogenic potential.

There was a positive Ames test result in the *Escherichia coli* tester strain WP2*uvr*A and the *Salmonella typhimurium* tester strain TA102 in the absence of metabolic activation. There was no evidence of a clastogenic effect in the *in vivo* mouse micronucleus assay.

In rats, fomepizole (110 mg/kg) administered orally for 40 to 42 days resulted in decreased testicular mass (approximately 8% reduction). This dose is approximately 0.6 times the human maximum daily exposure based on surface area (mg/m^2). This reduction was similar for rats treated with either ethanol or fomepizole alone. When fomepizole was given in combination with ethanol, the decrease in testicular mass was significantly greater (approximately 30% reduction) compared to those rats treated exclusively with fomepizole or ethanol.

Pregnancy:

Pregnancy Category C: Animal reproduction studies have not been conducted with fomepizole. It is also not known whether Antizol can cause fetal harm when administered to pregnant women or can affect reproduction capacity. Antizol should be given to pregnant women only if clearly needed.

Nursing Mothers:

It is not known whether fomepizole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Antizol® (fomepizole) Injection is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Safety and effectiveness in geriatric patients have not been established.

ADVERSE REACTIONS

The most frequent adverse events reported as drug-related or unknown relationship to study drug in the 78 patients and 63 normal volunteers who received Antizol were headache (14%), nausea (11%), and dizziness, increased drowsiness, and bad taste/metallic taste (6% each). All other adverse events in this population were reported in approximately 3% or fewer of those receiving Antizol and were as follows:

Body as a Whole: Abdominal pain, fever, multiorgan system failure, pain during Antizol injection, inflammation at injection site, lumbalgia/backache, hangover

Cardiovascular: Sinus bradycardia/bradycardia, phlebosclerosis, tachycardia, phlebitis, shock, hypotension

Gastrointestinal: Vomiting, diarrhea, dyspepsia, heartburn, decreased appetite, transient transaminitis

Hemic/Lymphatic: Eosinophilia/hypereosinophilia, lymphangitis, disseminated intravascular coagulation, anemia

Nervous: Lightheadedness, seizure, agitation, feeling drunk, facial flush, vertigo, nystagmus, anxiety, “felt strange”, decreased environmental awareness

Respiratory: Hiccups, pharyngitis

Skin/Appendages: Application site reaction, rash

Special Senses: Abnormal smell, speech/visual disturbances, transient blurred vision, roar in ear

Urogenital: Anuria

OVERDOSAGE

Nausea, dizziness, and vertigo were noted in healthy volunteers receiving 50 and 100 mg/kg doses of Antizol (at plasma concentrations of 290-520 μmol/L, 23.8-42.6 mg/L). These doses are 3-6 times the recommended dose. This dose-dependent CNS effect was short-lived in most subjects and lasted up to 30 hours in one subject.

Antizol is dialyzable, and hemodialysis may be useful in treating cases of overdosage.

DOSAGE AND ADMINISTRATION

Treatment Guidelines:

If ethylene glycol or methanol poisoning is left untreated, the natural progression of the poisoning leads to accumulation of toxic metabolites, including glycolic and oxalic acids (ethylene glycol intoxication) and formic acid (methanol intoxication). These metabolites can induce metabolic acidosis, nausea/vomiting, seizures, stupor, coma, calcium oxaluria, acute tubular necrosis, blindness, and death. The diagnosis of these poisonings may be difficult because ethylene glycol and methanol concentrations diminish in the blood as they are metabolized to their respective metabolites. Hence, both ethylene glycol and methanol concentrations and acid base balance, as determined by serum electrolyte (anion gap) and/or arterial blood gas analysis, should be frequently monitored and used to guide treatment.

Treatment consists of blocking the formation of toxic metabolites using inhibitors of alcohol dehydrogenase, such as Antizol, and correction of metabolic abnormalities. In patients with high ethylene glycol or methanol concentrations (≥ 50 mg/dL), significant metabolic acidosis, or renal failure, hemodialysis should be considered to remove ethylene glycol or methanol and the respective toxic metabolites of these alcohols.

Treatment with Antizol: Begin Antizol® (fomepizole) Injection treatment immediately upon suspicion of ethylene glycol or methanol ingestion based on patient history and/or anion gap metabolic acidosis, increased osmolar gap, visual disturbances, or oxalate crystals in the urine, **OR** a documented serum ethylene glycol or methanol concentration greater than 20 mg/dL.

Hemodialysis: Hemodialysis should be considered in addition to Antizol in the case of renal failure, significant or worsening metabolic acidosis, or equal to measured ethylene glycol or methanol concentration of greater than or equal to 50 mg/dL. Patients should be dialyzed to correct metabolic abnormalities and to lower the ethylene glycol concentrations below 50 mg/dL.

Discontinuation of Antizol Treatment: Treatment with Antizol may be discontinued when ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL, and the patient is asymptomatic with normal pH.

Dosing of Antizol:

A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours thereafter until ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL, and the patient is asymptomatic with normal pH. All doses should be administered as a slow intravenous infusion over 30 minutes (see **Administration**).

Dosage with Renal Dialysis: Antizol is dialyzable and the frequency of dosing should be increased to every 4 hours during hemodialysis.

Antizol Dosing in Patients Requiring Hemodialysis

Dose at the Beginning of Hemodialysis	
If <6 hours since last Antizol dose	If ≥6 hours since last Antizol dose
Do not administer dose	Administer next scheduled dose

Dosing during hemodialysis
Dose every 4 hours

Dosing at the time hemodialysis is completed	
Time between last dose and the end of hemodialysis	
<1 hour	Do not administer dose at the end of hemodialysis
1–3 hours	Administer 1/2 of next scheduled dose
>3 hours	Administer next scheduled dose

Maintenance dosing off hemodialysis
Give next scheduled dose 12 hours from last dose administered

Administration:

Antizol solidifies at temperatures less than 25° C (77° F). If the Antizol solution has become solid in the vial, the solution should be liquefied by running the vial under warm water or by holding in the hand. Solidification does not affect the efficacy, safety, or stability of Antizol. Using sterile technique, the appropriate dose of Antizol should be drawn from the vial with a syringe and injected into **at least 100 mL of sterile 0.9% sodium chloride injection or dextrose 5% injection.** Mix well. The entire contents of the resulting solution should be infused over 30 minutes. Antizol, like all parenteral products, should be inspected visually for particulate matter prior to administration.

Stability:

Antizol diluted in 0.9% sodium chloride injection or dextrose 5% injection remains stable and sterile for at least 24 hours when stored refrigerated or at room temperature. Antizol does not contain preservatives. Therefore, maintain sterile conditions, and after dilution do not use beyond 24 hours. Solutions showing haziness, particulate matter, precipitate, discoloration, or leakage should not be used.

HOW SUPPLIED

Antizol® (fomepizole) Injection is supplied as a sterile, preservative-free solution for intravenous use as:

Supplied in packages of four vials. Each vial contains 1.5 mL (1 g/mL) of fomepizole.

NDC 62161-003-34

Store at controlled room temperature, 20° to 25° C (68° to 77° F)

Distributed by:
Orphan Medical, Inc
Minnetonka, MN 55305

For questions of a medical nature, call 1-888-8ORPHAN (1-888-867-7426).

Part No. 4040265
Revision Date: December 2000

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