Forensic & Toxicology Team

MED 433

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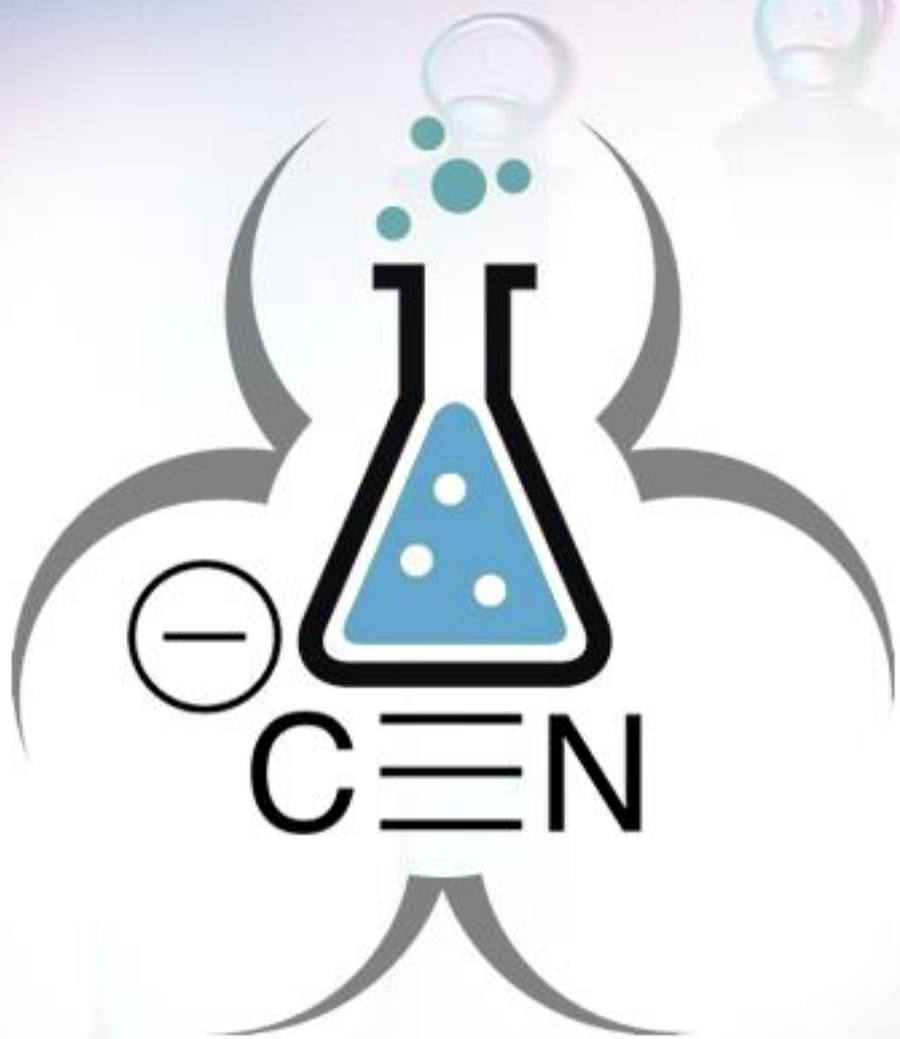


Lecture 11: Toxic Alcohols

Methanol

Perspective

Methanol is a colorless, volatile, slightly sweet-tasting alcohol.
Certain products found in the home, including :

Methanol can be found in:
Antifreeze; wind shield washer fluid; carburetor fluid; duplicator fluid; hobby engine fuel; gasohol; dry gas; sterno; glass cleaners; and thinners for shellacs, lacquers, adhesives, and inks may contain high concentrations of methanol.

*Treatment delay is associated with increased morbidity, making early recognition of clinical and laboratory clues crucial.

Additional notes :

- Methanol ,Ethylene glycol& Isopropyl alcohol : very toxic .
- Ethanol : non-toxic {Long-term use causes damage }.
- Alcohol intoxication :{ overdose } large amounts of ethanol can lead to Alcohol intoxication .

Principles of Disease:

Pharmacology and Metabolism

Prolonged half-life { 24 to 30 hours }.

**Gastric decontamination has a limited role and it's not useful .

The smallest lethal dose reported is 15 mL of 40% methanol
4 mL of pure methanol has led to blindness.

**Rapid absorption from the gastrointestinal tract, and blood levels peak 30 to 60 min after ingestion.

Small amounts of ingested methanol may be exceptionally toxic.

Transdermal and, respiratory tract absorption also has resulted in toxicity, especially in infants.

{ pediatric }the ingestion of only 1.5 mL of 100% methanol in a toddler (0.15 mL/kg) is sufficient to produce a toxic blood level of 20 mg/dL.

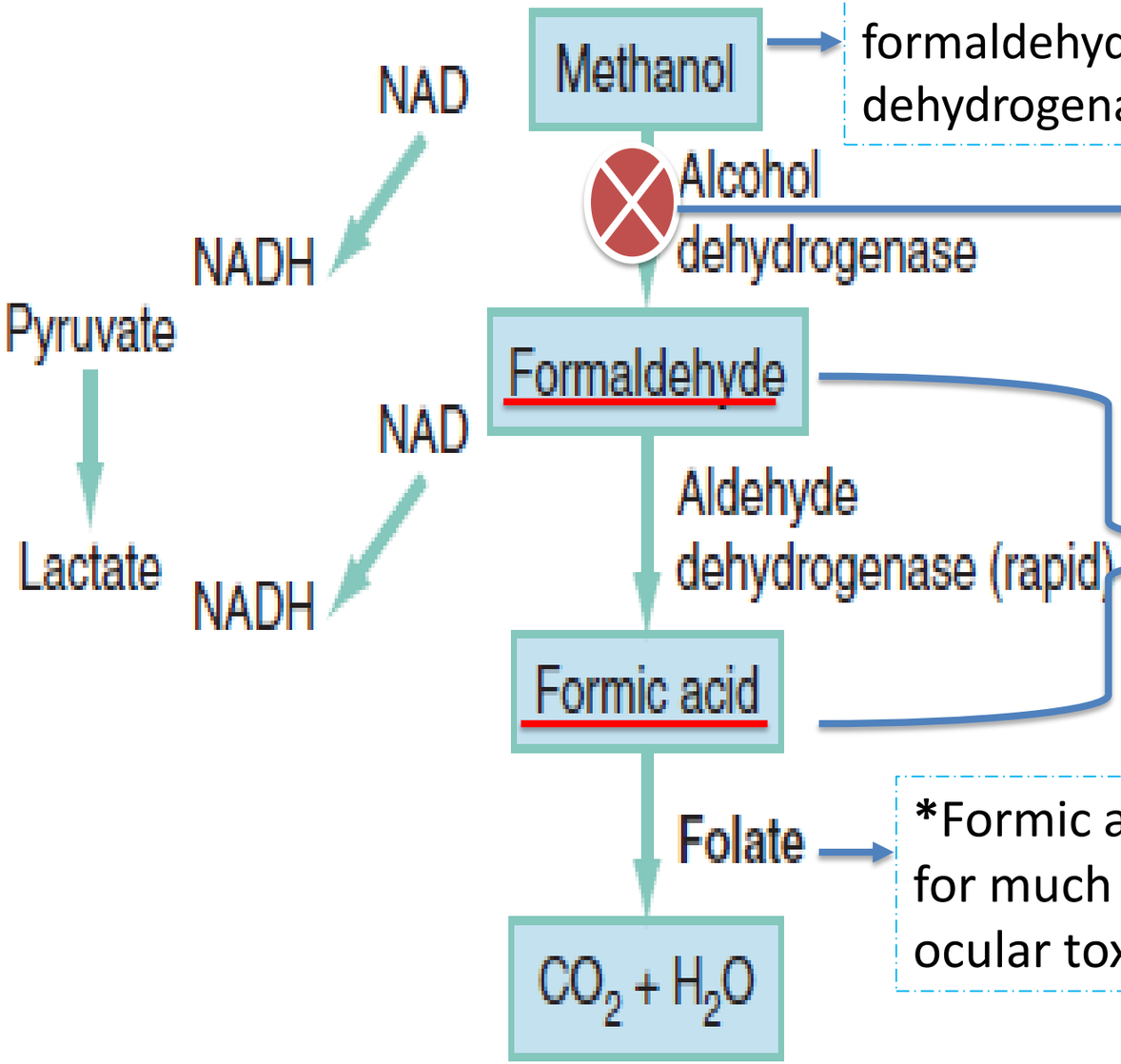
Inhalational abuse of methanol is a recent trend that can result in toxic serum levels.

Certain occupations, including painting, glazing, varnishing, lithography, and printing, are at high risk for inhalational exposure to methanol.

Metabolism of methanol

***Very important**

*Although small amounts of methanol are eliminated via renal and pulmonary routes, 90% is metabolized **hepaticaly.**



*Methanol is oxidized by alcohol dehydrogenase (ADH) to formaldehyde, which is rapidly converted by aldehyde dehydrogenase to formic acid.

Rx: Block the pathway

Metabolites of the parent alcohol are extremely toxic

*Formic acid is the primary toxicant and accounts for much of the anion gap metabolic acidosis and ocular toxicity peculiar to methanol ingestion.

*Through a folate-dependent pathway, formic acidis degraded to carbon dioxide and water.

Pathophysiology

Two main complications of severe methanol poisoning:

*__Optic neuropathy__

*__Putamen necrosis__

*Long-term morbidity takes the form of visual impairment, including blindness, and parkinsonian motor dysfunction, characterized by hypokinesis and rigidity.

*The primary sites of ocular injury are the retrolaminar optic nerve and retina.

*Lactate accumulation resulting from hypotension or seizures further compounds the metabolic acidosis predominantly caused by formate.

*Formic acid has a high affinity for iron and, as such, inhibits mitochondrial cytochrome oxidase, halting cellular respiration.

*Methanol metabolism in the cytosol & mitochondria may account for a second mechanism of adenosine triphosphate depletion.

Pathophysiology

*Acidosis may accelerate this process, by enhancing nonionic diffusion of formic acid into neurons and further increasing lactate production.

*Necrosis is described in the subcortical white matter, spinal cord anterior horn cells, and cerebellum.

*This self-perpetuating cycle of acidosis, termed circulus hypoxicus, underscores the need for aggressive correction of pH to accomplish ion trapping of formate outside the CNS.

Methanol adversely affects other areas of the CNS, specifically the basal ganglia.

*Bilateral, symmetrical putaminal hypodensities, hemorrhages, or cystic lesions are characteristic, occurring in 13.5% of patients.

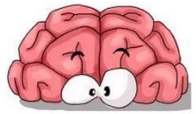
* Because methanol is a poor substrate for ADH, a latency period exists between the time of ingestion and onset of visual or metabolic disturbance.

*The typical 12- to 24-hour latency may be shorter when large amounts are consumed or longer when ethanol is co-ingested (range 40 min to72 hr).

*In patients who present early, formic acid accumulation may be ongoing, with risk for significant toxicity despite being asymptomatic.

Clinical Features





Early Symptoms:

CNS :

*Depressed mental status
*Confusion
*Ataxia
In severe cases, coma and seizures.

GIT :

Vomiting and abdominal pain common but their absence does not rule out a serious ingestion.

*Sluggishly reactive or fixed and dilated pupils indicate a poor prognosis.

*Pallor and cupping, indicative of optic atrophy, are late findings suggesting a poor prognosis for visual recovery.
*There may be tachypnea as a compensatory mechanism for acidosis

*cloudy, blurred, indistinct, or misty vision or may note yellow spots or, rarely, photophobia.

Nonspecific complaints:

*Weakness
*Dizziness
*Anorexia
*Headache
*Nausea

Clinical Features ”main”

* Altered mental status
* **Visual complaints** {50% of patients}
* Metabolic acidosis

Prognosis:

Correlate with the:

1- Degree of acidosis

2- Time to presentation

3- Initiation of treatment within 8 hours of exposure.

4- Coma, seizures

5-pH less than 7.0.

Patients surviving the acute phase of toxicity may be left with permanent blindness or neurologic deficits, such as parkinsonism, toxic encephalopathy, polyneuropathy, cognitive dysfunction, transverse myelitis, primitive reflexes, or seizures.

Diagnostic Strategies

*Severe anion gap metabolic acidosis

*The onset of acidosis may be delayed 12 to 24 hours, the presence of a normal anion gap does not rule out methanol exposure.

*Anion gap is due primarily to the presence of formic acid, with a variable contribution from lactic acid.

#Absence of high anion gap acidosis has been described in cases with :

*Ethanol

*Lithium

*Bromide ingestion

Diagnostic Strategies

>> High osmol gap

$$\text{Osmol gap} = \text{measured serum osmolality} - \text{calculated serum osmolality}$$

*It is the difference between measured serum osmolality and calculated serum osmolality.

$$\text{Calculated serum osmolality (mOsm/kg)} = 2(Na^+) + [BUN/2.8] + [glucose/18] + [ethanol(mg/dL)/4.6]$$

*The “normal” osmol gap is less than 10 mOsm/kg when the preceding equation is used.

*There is considerable variability in baseline osmolal gaps in patients, particularly children.

*An osmol gap significantly greater than 10 mOsm/kg may be a useful aid in the diagnosis of toxic alcohol ingestion.

Diagnostic Strategies:

*Caution should be taken in ruling out toxic alcohol ingestion with a “normal” osmol gap for several reasons.

*First, calculated serum osmolality results may vary among laboratories and must be done by the freezing point depression method.

*Delayed presentation after toxic alcohol ingestion may be associated with prior metabolism of most of the parent alcohol.

*Finally, a toxic level of either methanol or ethylene glycol may be present with a gap of only 10 mOsm/kg.

*serum toxic alcohol level is necessary
if not readily available, empirical treatment is warranted.

Diagnostic Strategies

*Rhabdomyolysis, pancreatitis, and metabolic derangements, such as hypomagnesemia, hypokalemia, and hypophosphatemia, are also described with methanol poisoning.

*The characteristic finding of bilateral putaminal lesions suggests methanol poisoning ,hypoxic-ischemic insult, encephalitis, and certain metabolic disorders.

*Ischemic necrosis, cerebral edema, or brain hemorrhages also may be noted.

*Follow-up scans may have prognostic value because parkinsonian features are unlikely to develop in patients whose putaminal lesions resolve within a short time frame.

***CT may be indicated in an intoxicated patient with altered mental status.**

***MRI may also detect putaminal aberrations or optic neuropathy from methanol intoxication.**

Differential Considerations

*Ethylene glycol and methanol may cause a “double gap” (i.e., an osmol gap in addition to the anion gap).

*Elevated osmol gap include isopropyl alcohol, ethanol, propylene glycol, mannitol, glycerol, and ethyl ether.

*Hyperlipidemia and hyperproteinemia, by decreasing the measured sodium concentration, can increase the osmolal gap.

Double-gap acidosis
may be encountered including :

*Diabetic ketoacidosis
*Alcoholic ketoacidosis
*Acetonitrile,methanol, ethylene glycol, and propylene glycol toxicity
*Multiple organ failure
*Chronic renal failure
* Critical illness

Differential Considerations

Diagnosis

identification of the parent alcohol in the blood by laboratory tests

Treatment

start treatment based on the clinical suggestion alone

Initial treatment for methanol and ethylene glycol is almost identical, identification of the specific toxic alcohol is not crucial to the initiation of therapy.

*Characteristically, isopropanol does not cause an increased anion gap.

Certain unusual characteristics of methanol and ethylene glycol intoxication lead to the specific diagnosis:

*The presence of ocular complaints unique to methanol poisoning is a valuable clue.

*Ethylene glycol ingestion often is associated with calcium oxalate crystalluria, which is not seen in methanol ingestion.

ETHYLENE GLYCOL

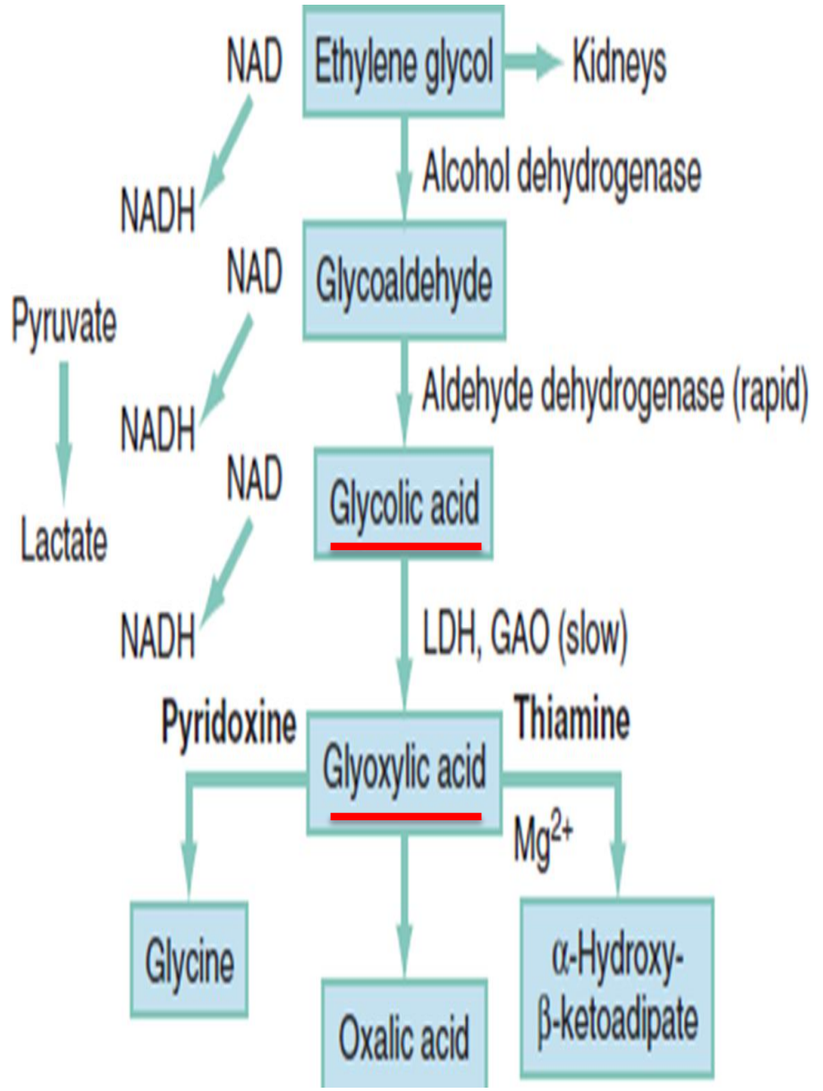
Perspective

- Most ethylene glycol poisonings occur with antifreeze.
- airplane deicing solutions, hydraulic brake fluids, and industrial solvents/precursors;
- it is in certain paints, lacquers, and cosmetics.

Pharmacology and Metabolism

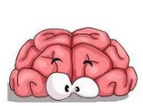
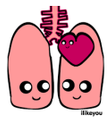
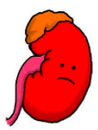
- Absorption of ethylene glycol is rapid after ingestion.
- Reported half-lives range from 3 to 8.6 hours.
- The toxic and lethal doses of 100% ethylene glycol have been reported as 0.2 mL/kg and 1.4 mL/kg.
- Twenty-seven percent of ethylene glycol is excreted unchanged by the kidneys.
- The remainder is hepatically oxidized via ADH and other oxidative enzymes to various toxic organic aldehydes and acids.

- Majority are 70% metabolized in the liver and 30% excreted unchanged in urine



Pathophysiology

- 2.3%of a dose of ethylene glycol ultimately is converted to oxalic acid, most of which is excreted in the urine.
- A fraction of oxalic acid combines with calcium to form calcium oxalate crystals, which precipitate in renal tubules, brain, and other tissues.
- The metabolism of ethylene glycol results in a profound anion gap metabolic acidosis caused mainly by glycolic acid.

Clinical Features  +  + 

- **acute neurologic stage**(occurs 30 minutes to 12 hours after ingestion)
- **cardiopulmonary stage** (occurs 12 to 24 hours after ingestion)
- **renal stage** (occurs 24 to 72 hours after ingestion)
- **delayed neurologic sequelae stage** (occurs 6 to 12 days after ingestion)

*Patients may die in any stage

- Metabolic acidosis and symptoms typically occur within 4 to 8 hours, but may be delayed for 12 hours or longer if ethanol has been co-ingested.

Late presentation (need more time for toxic metabolites to be formed and accumulated 2 days)

Poor prognostic factors include :

- Hyperkalemia
- severe acidosis
- Seizures
- coma

Diagnostic Strategies

- serum electrolytes, calcium, BUN, creatinine,
- serum glucose,
- serum osmolality, blood ethanol level,
- ABG
- ethylene glycol level
- Electrocardiogram
- urinalysis. crystalluria is considered the hallmark of ethylene glycol ingestion, its absence does not rule out the diagnosis.
- profound anion gap metabolic acidosis when the metabolites glycolic acid and glyoxylic acid (and, to some extent, lactic acid) accumulate. (acidotic breathing)
- elevated osmolal gap as measured by freezing point depression is a clue to the diagnosis of ethylene glycol toxicity.
- CT and MRI.

Management

- Methanol and ethylene glycol ingestions are treated essentially the same.
- Decontamination is not useful

Management

3 objectives in methanol or ethylene glycol toxicity treatment: ABC first

(1) correction of metabolic acidosis with bicarbonate.
(2) ADH enzyme blockade, which inhibits the metabolism of methanol and ethylene glycol to toxic metabolites either by ethanol* or fomepizole (Antizol).
(3) removal of the parent alcohol and its metabolites by hemodialysis.

Fomepizole (ANTIDOTE)

- MOA: **blocks the metabolism of methanol and ethylene glycol by ADH and prevents the formation of toxic metabolites**.
- When methanol or ethylene glycol metabolism is blocked by fomepizole, their half-lives increase to an average of 52 and 17 hours, respectively.
- Fomepizole is a pregnancy category C drug.
- S/E: inflammation at the site of infusion, rash.

Hemodialysis

Indications :

- metabolic acidosis
- renal compromise
- visual symptoms (methanol)
- deterioration despite intensive supportive care
- electrolyte imbalances
- unresponsive to conventional therapy.

*ethanol (b/c of its higher affinity to alcohol dehydrogenase enzyme) effective as the antidote NGT OR I.V. form.

- In ethylene glycol we give cofactors thiamine and pyridoxine.
- IV calcium With symptomatic hypocalcemia.
- Magnesium is a cofactor along with thiamine.

ISOPROPYL ALCOHOL (isopropanol)

Perspective:

Isopropyl alcohol (isopropanol) is a clear, colorless liquid with a slightly bitter taste.

It is the second most commonly ingested alcohol after ethanol.

Rubbing alcohols, which contain 70 to 91% isopropanol or ethanol, are frequent sources.

skin and hair products, nail polish removers, disinfectants, window and pine household cleaners, and antifreeze.

Isopropanol and its major metabolite acetone cause **CNS depression.**

Typical fatality involves a chronic, older alcoholic with mixed ethanol-isopropanol intoxication after a drinking binge.

Absorption of isopropanol is rapid and complete; 80%of a dose is absorbed within 30 minutes of ingestion.

The kidneys excrete 20% as unchanged isopropanol.

A small portion is resecreted into the stomach and saliva.

the remaining 80% is metabolized in the liver to acetone by ADH.

Acetone is excreted primarily by kidneys, with small amounts expired through the lungs.

blood levels peak 30 minutes to 3 hs after.

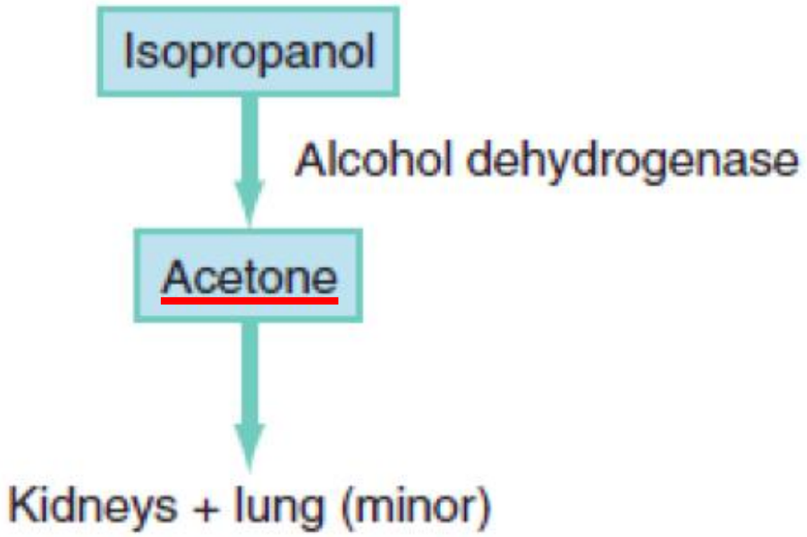
elimination with a half-life of 3 to 7 hours.

In children, the half-life may be slightly shorter.

Acetone is eliminated more slowly, with a half-life of 22 hours.

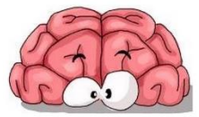
A potentially lethal dose in adults is **150 to 240 mL (2–4 mL/kg)**

Metabolism of isopropanol



Pathophysiology

Isopropanol is a potent CNS depressant, but the mechanism of action is unclear.
Acetone is also a CNS depressant
In large doses, isopropanol causes hypotension from peripheral vasodilation and direct myocardial depression.
Topical effects include corneal de-epithelialization or dermal burns.
Acetone does not seem to be shunted into the formation of acetoacetate or β-hydroxybutyrate;
The finding of ketosis without acidosis is characteristic of isopropyl ingestion.

Clinical Findings  + 

 # GI and CNS predominate.

Odor of acetone rather than ethanol detected on the breath.

Headache or dizziness and may exhibit neuromuscular incoordination, confusion, and nystagmus.

Severe ingestions may result in deep coma, which is prolonged compared with ethanol.

Loss of deep tendon, corneal, or protective airway reflexes.

Extensor response to plantar reflex testing.

Pupillary size varies, miosis is most common.

Abdominal pain, nausea, and vomiting.

Gastritis can occur with dermal and oral exposure.

Hypotension with a mortality rate of 45%.

Sinus tachycardia is common.

Atrial and ventricular dysrhythmias are rare

Hypothermia is frequent.

Rarely, myoglobinuria, acute tubular necrosis, hepatic dysfunction, and hemolytic anemia have been reported.

Metabolic acidosis is not present

Hyperglycemia may be noted.

Diagnostic Strategies

serum electrolytes, BUN, creatinine
Osmolality
serum and urine ketones
#ABG
A CK (creatine kinase) level should be checked because patients with isopropanol toxicity may have coma-induced myoglobinuria and rhabdomyolysis.

isopropanol level peaks occur soon after ingestion.
acetone levels peak **4 hours** after ingestion.
The most common laboratory abnormality is ketosis with little or no acidosis and normal blood glucose levels.
ketosis is from the metabolite acetone, which can be detected in the blood 15 minutes after ingestion and in the urine 3 hours after ingestion.
isopropanol and acetone contribute to the increased osmol gap.
1-mg/dL increase in blood isopropyl alcohol concentration should result in a 0.17-mOsm/kg increase in serum osmolality.
falsely elevate creatinine without high urea.
Creatinine is expected to increase 1 mg/dL for every 100 mg/dL of acetone.

Management and Disposition

>> supportive

#Neither gastric emptying

#Hypotension should be managed with fluids and vasopressors as needed.

If the patient remains hypotensive or has further vital sign deterioration despite these measures, **dialysis is indicated**.

Some authors also recommend dialysis for isopropanol serum levels greater than 400 mg/dL

KEY CONCEPTS

- Small doses (single swallows) of methanol and ethylene glycol may cause toxicity.
- A latent period before the development of symptoms is characteristic for ethylene glycol and methanol toxicity, especially when ethanol has been co-ingested.
- A double-gap acidosis (anion gap and osmol gap) should suggest methanol or ethylene glycol toxicity.
- Toxic alcohol exposure cannot be ruled out by a "normal" osmol gap.
- Therapy should begin immediately based on clinical suspicion of exposure to ethylene glycol or methanol. Acidosis should be corrected rapidly with bicarbonate, cofactors should be administered, and ADH should be blocked with ethanol or fomepizole.
- Because acidosis in the setting of exposure to either substance indicates toxic metabolite accumulation, immediate consultation for hemodialysis should be made, even before laboratory confirmation of toxic ethylene glycol or methanol levels.
- The presence of an osmol gap without acidosis is characteristic of isopropanol ingestion. Prolonged coma may be seen, and hypotension portends a poor prognosis.

QUESTIONS:

Q1- which of the following is considered a non-toxic alcohol:

A- ethylene glycol
B- ethanol
C- methanol
D- isopropyl alcohol

Q2- a 33 years old man is brought to the ED with altered mental status ,flank pain, the man works in an airport and has an access to ethylene glycol, toxicity with ethylene glycol is suspected , how would you approach this patient "first step" ?

A- ECG
B- urinalysis
C- ABC
D- hemodialysis

Q3- Regarding methanol poisoning:
#Assertion: Administration of ethanol is one of the treatment modalities.
#Reason: Ethanol inhibits alcohol dehydrogenase .
Please select the most correct option from the following:

A- Both assertion and reason are true, and the reason is the correct explanation for the assertion
B- Both assertion and reason are true, and the reason is not the correct explanation for the assertion
C- Assertion is true, but the reason is false
D- Assertion is false, but the reason is true

Q3- the difference between (methanol / ethylene glycol) and (isopropanol) intoxication is the :

A- presence of CNS symptoms
B- metabolic alkalosis
C- ketosis
D- increased osmolar gap.

Ans:
1-b
2-c
3-a
4-c

If you have any questions You can always contact us at :
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