Alcohols

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Ethanol

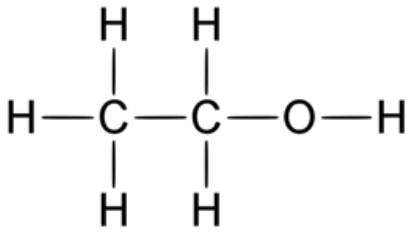
- Ethanol intoxication appears when consumption exceeds individual's tolerance
  - Results in behavioral or physical abnormalities (including mental and physical abilities are impaired).
  - Ethanol determination is the most frequently performed test in Forensic Toxicology laboratories
  - Most common single substance taken by patients visiting emergency departments.

-Leading killer of people aged 15 to 45 years and is associated with 67% of drownings, 70% of fire deaths, 67% of murders, 35% of suicides, and the vast majority of deaths from hepatic failure.

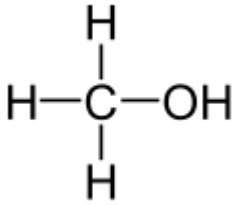
For untreated alcoholics, normal life expectancy decreases 12 to 15 years

-Prompt recognition and management reduce morbidity and mortality.

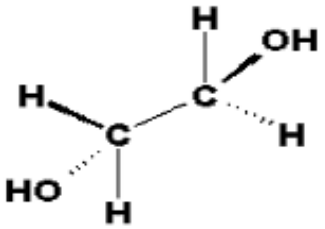
- Ethanol



- Methanol



- Ethylene glycol



Ethanol

It’s a clear, aliphatic hydrocarbon.

Universal diluent found in alcoholic beverages

Solvent, and fuel

Ingredient in food extracts, cough and cold medications, and mouthwashes.

-Distilled spirits typically contain ethanol volumes of 40% to 50%

-Wines : vary more widely in ethanol content ranging from 10% to 20%

-Beers : 2% to 6% ethanol

-Mouthwashes may contain up to 75% ethanol

-Colognes : up to 40% to 60% ethanol.

- Medicinal preparations contain ethanol as an inert diluent or solvent : 0.3% to 68%

Pathophysiology

-CNS depressant, electively depresses reticular activating system

-Frontal lobes are sensitive to low concentration then it affects the occipital lobes where visual changes occur and finally cerebellum causing lose of coordination

-Binds directly to gamma-aminobutyric acid (GABA) receptor in the CNS

-Direct effects on cardiac muscle, thyroid tissue, and hepatic tissue.

Chronic Effects

-Decreases (NAD+ /NADH) ratio ## alter cellular redox .

-Shift from pyruvate to lactate ## acidosis.

Pyruvic Acid + NADH + H^+ ---> Lactic Acid + NAD^+

-Elevation of serum uric acid ## reduced clearance.

-Alter lipid metabolism ##to accumulation of fat in the liver, Increase collagen deposition, decrease protein synthesis .

ABSORPTION

- Ethanol is rapidly absorbed
  - Starts in the oral mucosa
  - Continues in gastric mucosa (20 %) and the small intestines (80 %)
  - Reaches a peak concentration 30-60 minutes after ingestion.

DISTRIBUTION

-Both water and lipid soluble, ethanol distributes into total body water and so Easily penetrates the BBB and placenta.

-Volume of distribution is ~ 0.6 L/kg in adults and 0.7 L/kg in children.

-Women have a smaller Vd than men.

ELIMINATION

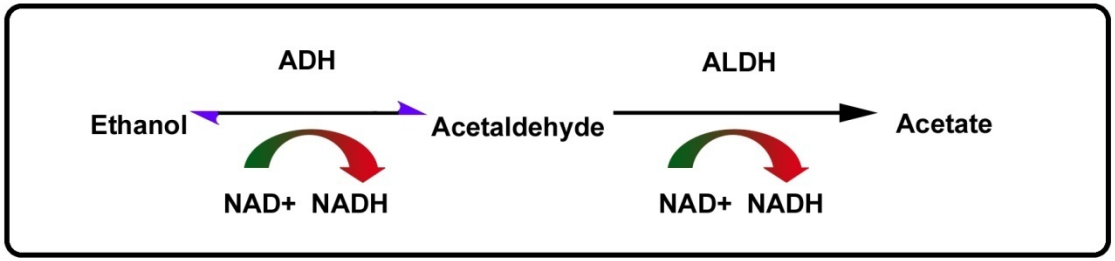
-Hepatic metabolism is characterized by **zero-order kinetics** except at very low or very high concentrations.

-It's 1ry metabolized in the liver (90%) ; the remainder (~ 5-10%) is eliminated by the kidneys and lungs unchanged .

- Blood ethanol decreases more rapidly at concentrations over 300 mg/dL, because of oxidation by the microsomal ethanol-oxidizing system.
- Average adult metabolizes 7 to 10 g/h and reduces the ethanol level 15 to 20 mg/dL/h.
- Alcoholics, have metabolic rates as high as 30 to 40 mg/dL/ h.

Metabolism

1 - the cytosol-based enzyme alcohol dehydrogenase (ADH): major



2- A microsomal ethanol-oxidizing system MEOS in the Endoplasmic reticulum. imp. For high concentrations.

3 - A peroxidase-catalase system is a minor pathway located in peroxisomes.

Manifestations

-Hypoglycemic state mainly in young children.

- CNS depression, irritability, drowsiness, stupor, and coma

-Respiratory depression and hypoxia

-Change in mental status

-Hypothermia

-Cognitive and psychomotor skills behavioral abnormalities

-slurred speech, ataxia, gait disturbances

-flushed face

-Evaluation for signs of trauma, neglect, and illicit drug use

- dysrhythmias

-decreased preload, after load, and systemic vascular resistance

- Heavy consumption (> 400 gm / wk) of alcohol appears to Predispose to both hemorrhagic and nonhemorrhagic strokes.

-Urticaria

-Inhibition of spermatogenesis.

- Fetal alcohol syndrome
- Malnutrition
- Obesity
- **Vitamin deficiencies of Bl, B6, B12, zinc, and *magnesium***

Neurologic impairment depends on:

1) Genetic factors
2) Amount ingested
3) Prior alcohol use
4) Co-ingestion of other drugs and alcohol products

Disulfiram reaction

- When some drugs are taken with alcohol by interfering aldehyde dehydrogenase.
- Metronidazole, Sulfonamides, hypoglycemia agents.
- Manifest as: Nausea, vomiting, flushing of the skin, tachycardia (accelerated heart rate), and shortness of breath.

Laboratory Investigation

1- Serum Glucose Level – hypoglycemia

2- Electrolyte levels : The anion gap measurement should be determined. Acute ethanol intoxication usually does not cause significant anion gap metabolic acidosis.

3- Ethanol level

- Ethanol blood levels roughly correlate with clinical signs.
- Urine second void sample
- Breath once mouth is clear
- Add sodium fluoride preservative to urine or blood samples

Treatment

-ABCs .

- Correct Hypoglycemia & hypothermia.

-Correct electrolyte and fluid abnormality.

- Prevent.

-Decontamination unhelpful due to rapid absorption

-Thiamine to prevent Wernicke korsakoff syndrome

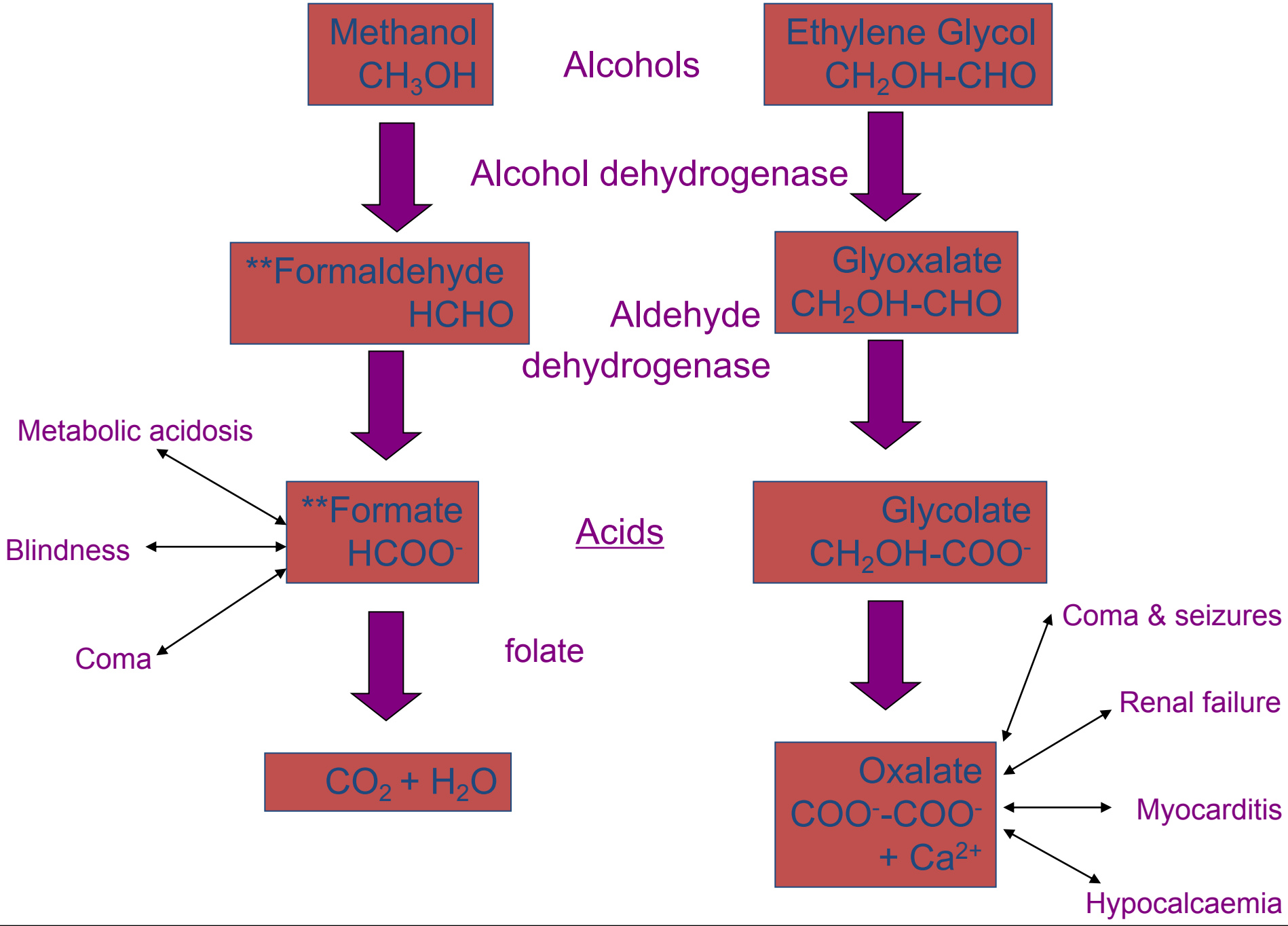
Others :

- In patients with chronic ethanol abuse, administer **thiamine 100 mg** IV/IM - prior to glucose load - to prevent neurologic injury,.
  - –(Thiamine def. in chronic alcoholics. Manifested by ataxia and nystagmus, and Korsakoff's psychosis with anterograde and retrograde amnesia and confabulation upon relevant lines of questioning.)

In chronic alcoholic: Magnesium sulfate, Thiamine, Folate, Multivitamins.

Methanol

- Colorless, volatile liquid, CH3OH
- Gas Line Antifreeze 100%
- Windshield washer fluid 30%
- Paint thinners, paints
- Fuel for food warming 3-70%
- Industrial uses


Methanol
CH_3OH
Alcohols
Ethylene Glycol
CH_2OH-CHO
Alcohol dehydrogenase
**Formaldehyde
HCHO
Glyoxalate
CH_2OH-CHO
Aldehyde
dehydrogenase
Metabolic acidosis
Blindness
Coma
**Formate
$HCOO^-$
Acids
Glycolate
CH_2OH-COO^-
folate
Coma & seizures
Renal failure
Myocarditis
Hypocalcaemia
$CO_2 + H_2O$
Oxalate
COO^--COO^-
+ Ca^{2+}

- CNS depressant similar to ethanol.

Lactate may appear late in the course in severe poisoning due to inhibition of mitochondrial respiration and tissue hypoxia.

- **Absorption:**

- GI, also skin and lungs
- Peak levels in 30 to 90 min

- **Distribution**

- like ethanol 0.7L/kg
- Highest concentrations GI, liver, kidneys
- Vitreous humor and optic nerve

- Elimination:
  - Hepatic mostly
  - It is oxidized 10 times more slowly than ethanol
  - Ethanol has 10 to 20 times greater affinity for alcohol dehydrogenase than methanol.
  - Half life after mild toxicity is 14 to 20 h

Clinical presentation

- Latent period is 12 to 24 hours
- CNS depression manifestation.
- Cerebral edema
- Eyes: blurred vision, photophobia, retinal edema
- Metabolic acidosis, dyspnea, shock, coma, seizures
- Death from respiratory arrest

Progression:

- Severe headache
- Blurred vision
- Severe abdominal pain
- Vomiting
- Seizures, coma

Visual symptoms:

- Initial early reversible retinal dysfunction,
- Eventual irreversible optic neuropathy 25% persist

- 1 ml/ kg is considered lethal, but with wide individual variation
- CNS symptoms appear above 20 mg/dl
- Ocular symptoms 100 mg/dl
- Death if untreated 150 to 200 mg/dl
- Ethanol reduces methanol toxicity
- Mortality correlates best with severity of acidosis rather than methanol levels.

Management

- Gastric Lavage if presenting early
- Activated Charcoal not applicable
- Forced diuresis isn’t effective

Hemodialysis

- Considered integral part of treatment
- removes of alcohol and its toxic metabolites
- Reduces necessary duration of antidotal treatment
- Both ethylene glycol & methanol effectively cleared by HD

Antidotes

- **Ethanol:** Competitively occupies Alcohol dehydrogenase (**ADH)**, to reduce toxic metabolite
- Accepted target 100-125 mg/dL to completely inhibit toxic metabolite formation
- Indications:
  - Methanol >20mg/dl, Symptomatic patient
  - Being considered for Hemodialysis
  - Metabolic acidosis
- **Fomepizol**: inhibits ADH
- Folate as cofactor for the oxidation of formic acid to CO2

Ethylene Glycol

- Odorless, colorless, nonvolatile liquid having a sweet taste.
- Weakly toxic, but cases of poisonings are not uncommon.
- Small amounts of ingested can be fatal.
- Encountered around the home as automotive antifreeze.

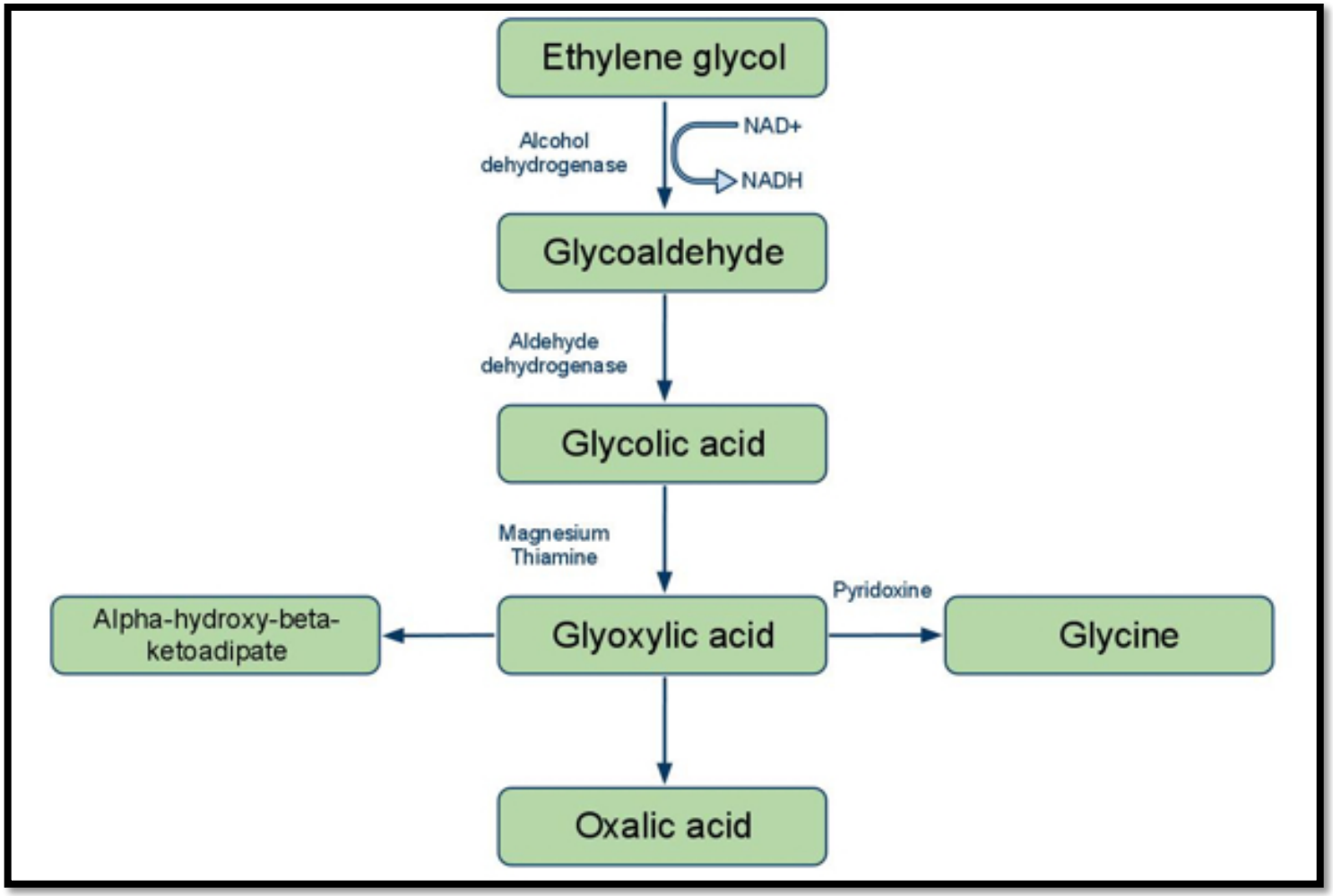
- Commonly ingested because of its sweet taste and the “lemonade” appearance of many antifreeze products and because it is readily available to inquisitive children from carelessly stored containers of antifreeze in the garage.
- Consumed by adults for purposes of inebriation which, in its early stages, resemble that of ethanol .

Mechanism of Toxicity

- Converted to metabolite that is more toxic than the parent compound.
- Highly water-soluble and rapidly absorbed when ingested
- Peak blood levels occur within 1 to 4 h of an ingestion.
- Plasma half-life is 3 to 5 h.

- Metabolized AHD to glycol aldehyde which is rapidly metabolized to glycolate and Oxalic acid.
- Metabolites are responsible for tissue destruction
- Deposition of calcium oxalate crystals
- Severe metabolic

- Glycolate is metabolized by various pathways, including one to oxalate which rapidly precipitates with calcium in various tissues and in the urine.



Clinical Manifestation

- The target systems are: CNS, Cardiac and respiratory and Renal systems**.**
- Initially CNS depression
- Other:

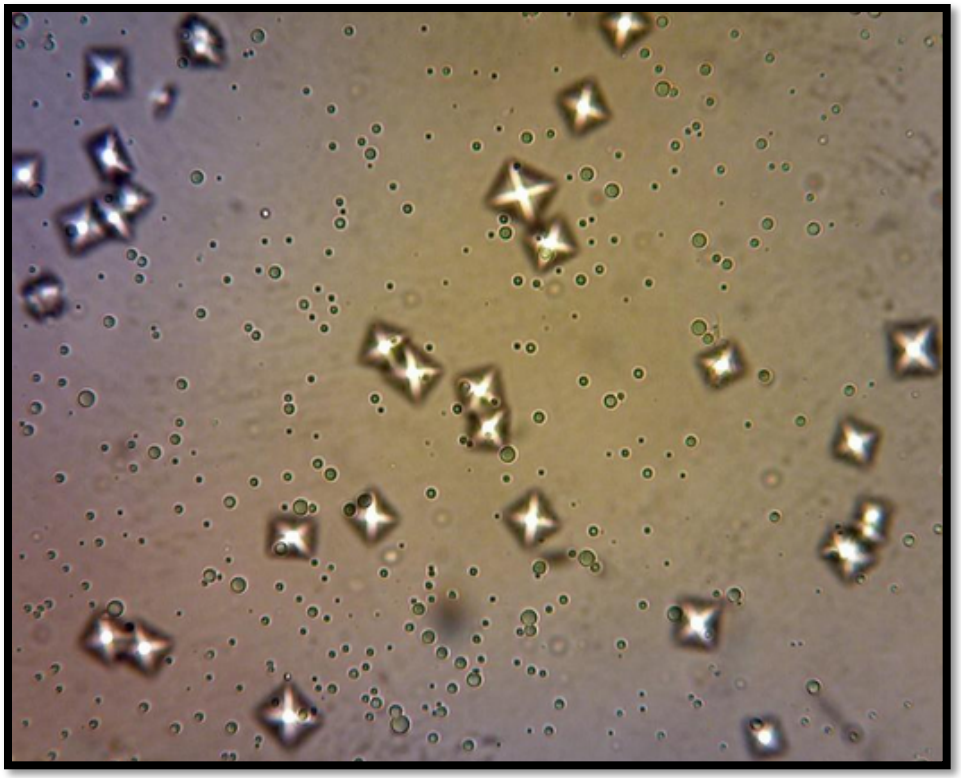
1. Muscle paralysis.
2. Decreased tendon reflexes.
3. Convulsions.
4. Tetany (hypocalcemia).

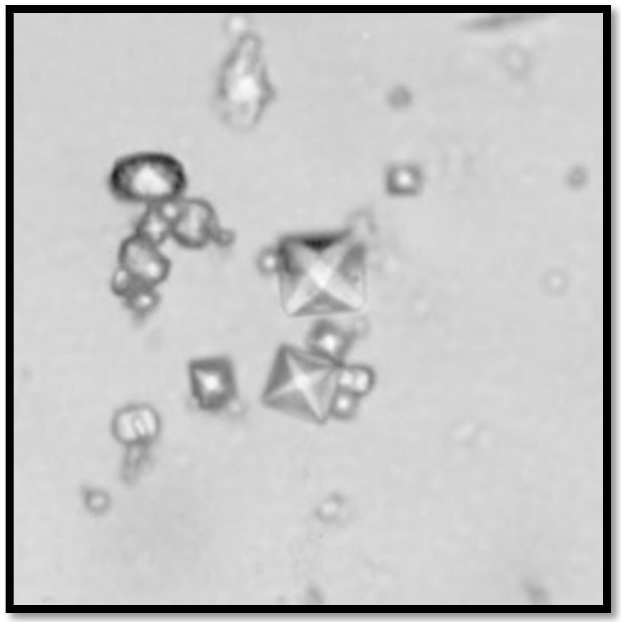
These effects are usually starts:

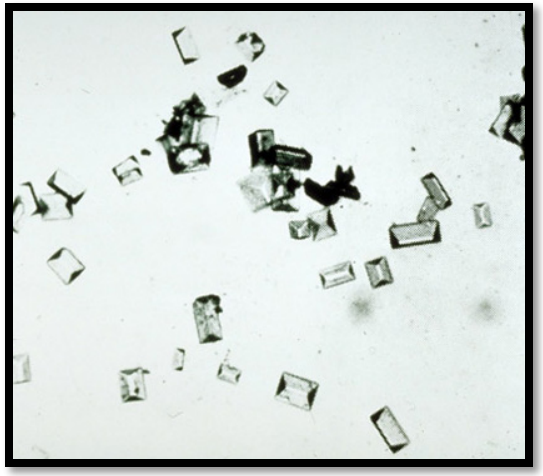
Vomiting, ataxia, stupor, nausea, coma, Hallucinations, seizures and Death, (depending on the amount ingested), during this initial phase.

- Second, cardiopulmonary phase develops 12 to 24 h after ingestion.
- Tachycardia, mild hypertension, and tachypnea
- Pulmonary edema
- Congestive heart failure.
- Tachycardia.
- Renal failure develop as a result of calcium oxalate crystals deposition.

- Third phase (24 to 72 hours) onsist of flank pain and costovertebral angle tenderness.
- Oliguric renal failure and acute tubular necrosis
- Kidneys are susceptible due to deposition of calcium oxalate crystals in renal tubules leading to tubular epithelial necrosis with fat inclusion, particularly in the convoluted tubules.
- Glomeruli develop thickened basement membranes and granule deposits.







Calcium Oxalate in Urine

Investigations

- EG levels
- ABG
- ECG
- Urine analysis
- KFT

Treatment

- Correct acidosis and convulsion
- Calcium gluconate for hypocalcemia
- Monitor cardiac function
- **Ethanol** to compete EG on ADH
- Or **Fomepizol** as ADH inhibitor dehydrogenase .
- Gastric lavage
- Hemodialysis
- Pyridoxine and thiamine to facilitate metabolism of ethylene glycol by non toxic pathway