

Emergency Medicine Clinical Pearls

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Objectives

- Describe the steps involved in rapid sequence intubation
- Define the role of N-Acetylcysteine in the treatment of acetaminophen overdose
- Explain treatment strategies for toxic alcohol ingestion

Rapid Sequence Intubation (RSI)

- The nearly simultaneous administration of a potent intravenous anesthetic agent and neuromuscular blocking agent to facilitate endotracheal intubation.

Pharmacist's Role in RSI

- Drugs available
- Drug doses
- Contraindications / precautions
- Onset of action
- Duration of action
- Logistics

The 7 P's + 1 I

- Preparation
- Pre-oxygenation
- Pretreatment
- Induction
- Paralysis
- Protection
- Placement
- Post-intubation management

Pretreatment

- Why?
 - Noxious stimuli Pressor response
 - Increased sympathetic activity
 - Increased heart rate, blood pressure, ICP
- LOAD
 - Lidocaine
 - Opiates
 - Atropine
 - Defasciculating agent

Lidocaine

- 1.5 mg/kg 2-3 min prior to intubation
- May blunt cardiovascular and cough responses
- Attenuates ICP and IOP increases
- Blunts fasciculations induced by succinylcholine
- Antidysrhythmic
- Use is somewhat controversial

Vallinovsky C. Ann Emer Med. 2007 Jan;49(1):86-7.
Wadbrook P. Emer Med Clin Namer. 2000 Nov;18(4):767-88.
Weingart S. Ann Emer Med. 2007 Jan;50(3):353.

Opiates

- Fentanyl: 1.5 3 mcg/kg
- Attenuate the hyperdynamic CV responses to laryngoscopy and intubation
 - Little effect on tachycardia
- Analgesia
- May blunt increase in ICP
- Rapid IV push may lead to truncal muscle rigidity
 - Related to rate of infusion

Wadbrook P. Emer Med Clin Namer. 2000 Nov;18(4):767-88.

Atropine

- 0.01-0.02 mg/kg IV push
- May prevent bradycardia
 - Pharynx stimulation = vagal response
 - Succinylcholine systemic cholinergic effects
- Used primarily in pediatric population
 - < 10 yo)
- Suggested for adults receiving 2nd dose of succinylcholine
- Decreases respiratory secretions

Frakes MA. J Emer Nurs. 2003 Dec;29(6):533-40.
Rubin M et al, in Emergency Medicine: A Comprehensive Study Guide - 6th Ed. (2004)

Defasciculating Agent

- Generalized, involuntary muscle fiber contractions that cause visible twitching but not joint movement
- Associated with succinylcholine use
- Increased ICP, aspiration, and IOP
- Premedication with 10% of intubating dose of a non-depolarizing neuromuscular blocker
 - Vecuronium: 0.01 mg/kg
 - Rocuronium: 0.1 mg/kg
- Lidocaine

Rubin M et al, in Emergency Medicine: A Comprehensive Study Guide - 6th Ed. (2004)
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Induction

- Agent should produce rapid unconsciousness without altering hemodynamics
- Need to consider:
 - Preexisting cardiovascular, intracranial, or reactive airway disease
 - Hyper / hypotension
 - Hypovolemia
 - Multiple trauma
- Recommended for all patients
- Must consider time to onset and duration of action

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Sedative Agents

Agent	Dose	Onset / Duration	Pros	Cons
Etomidate	0.3 mg/kg IVP	30 sec / 7-15 min	Pharmacodynamics CV stable Decrease ICP & IOP	Adrenocortical suppression Myoclonus, pain on injection No attenuation sympathetic response
Thiopental	2-5 mg/kg IVP	30-60 sec / 5-10 min	Pharmacodynamics Decrease ICP & IOP	Hypotension Histamine release Bad if extravasates
Ketamine	1-2 mg/kg IVP 4-5 mg/kg IM	30-60 sec / 5-10 min	Pharmacodynamics Analgesic / amnestic	Increased sympathetic outflow Emergence phenomenon
Propofol	1-2.5 mg/kg IVP	30 sec / 5-10 min	Pharmacodynamics Decreased ICP & IOP Amnestic Depression of laryngeal & pharyngeal reflexes	Dose-related hypotension

Paralysis

- Immediately follows induction
- Facilitates optimal visualization, confers easier patient manipulation, reduces complications
- Ideal agent has rapid onset, short duration, minimal hemodynamic effects, and few systemic side effects
- Depolarizing vs. non-depolarizing agents

Rubin M et al. in Emergency Medicine: A Comprehensive Study Guide - 6th Ed. (2004)
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Succinylcholine

- Only depolarizing agent
- Dose: 1-2 mg/kg IV push (1.5 mg/kg)
- Onset: 45-60 sec. Duration: 5-10 min.
- Hyperkalemia
 - Burn, multiple trauma, neuromuscular disease, shock and metabolic acidosis, crush injuries, chronic renal failure, myopathy
 - Typically occurs weeks to months after initial acute disease process or event.

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Succinylcholine

- Bradycardia
 - Pediatric patients and after repeat dose in adults
 - Atropine may mitigate
- Increased IOP and ICP
 - Transient
- Fasciculations

Rubin M et al. in Emergency Medicine: A Comprehensive Study Guide - 6th Ed. (2004)
Wadbrook P. Emer Med Clin Namer. 2000 Nov;18(4):767-88.

Non-Depolarizing NMBs

- Competitively bind to Ach receptors preventing muscular depolarization
- Rocuronium:
 - Dose: 0.6 mg/kg IV push
 - Onset: 30-120 sec. Duration: 30-45 min.
 - Higher dose may decrease onset time
- Vecuronium:
 - Dose: 0.1 mg/kg IV push
 - Onset: ~ 3 min. Duration: 30-45 min.

Rahin M et al. in Emergency Medicine: A Comprehensive Study Guide - 6th Ed. (2004)
Wadbrook P. Emer Med Clin Namer. 2000 Nov;18(4):767-88.

Paralytic Agents

Agent	Dose	Onset / Duration	Pros	Cons
Sux	1.5 mg/kg IVP	45-60 sec / 5-10 min	Pharmacodynamics	Hyperkalemia Bradycardia Fasciculations Increased ICP & IOP
Rocuronium	0.6-1 mg/kg IVP	30-120 sec / 30-45 min	Alternative to sux Quick onset	Duration
Vecuronium	0.1 mg/kg IVP	3 min / 30-45 min	Alternative to sux	Long onset / duration

Postintubation Management

- Sedation
 - Continuous infusion of sedative agent
 - Titrate to desired effect
- Paralytic
 - Does not provide any analgesia or sedation

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Summary

- Knowing doses, onset and duration of action of all agents is imperative
- Intubation induces a sympathetic response
- All medications used have side effects that require consideration before use

Acetaminophen Toxicity

Acetaminophen

- First clinically used in U.S. in 1950
- Possesses analgesic & antipyretic activity
- > 100,000 calls to U.S. poison centers each year from potential exposures
- Poisoning can be from single overdose, excessive repeated doses, or too frequent doses.
- More hospitalizations from overdose than any other common medication

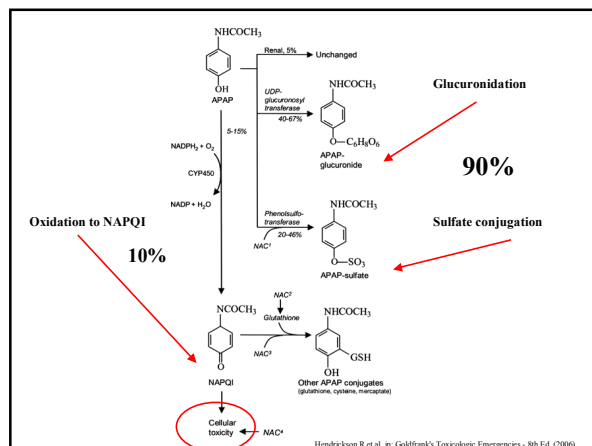
Acetaminophen

- Found in combination with many other drugs
 - Hydrocodone
 - Codeine
 - Tramadol
 - Oxycodone
 - Butalbital
 - Chlorpheniramine
 - And the list goes on □ □ .

Pharmacokinetics

- Rapidly absorbed
 - Time to peak levels 30 - 45 min.
- PO bioavailability: 60-98%
- 1st pass metabolism removes ~ 25%
- Normal elimination half-life: 2-3 hrs.

Hendrickson R et al. in: Goldfrank's Toxicologic Emergencies - 8th Ed. (2006)



NAPQI

- Extremely hepatotoxic
- Rapidly detoxified with glutathione (GSH)
- Acetaminophen overdoses can deplete GSH supply

Hendrickson R et al. in: Goldfrank's Toxicologic Emergencies - 8th Ed. (2006)

Toxicokinetics

- Majority of drug absorption within 2 hrs.
- Peak plasma concentrations within 4 hrs.
- Overall elimination is prolonged

Hendrickson R et al. in: Goldfrank's Toxicologic Emergencies - 8th Ed. (2006)

Pathophysiology

- Hepatic toxicity when hepatic GSH falls to < 30% baseline.
- NAPQI covalently binds to cell proteins resulting in cell death
 - DNA fragmentation, increased mitochondrial permeability, and mitochondrial injury
- Binding process can be reversed
- Renal injury may also occur
 - Renal CYP2E1 formation of NAPQI

Hendrickson R et al. in: Goldfrank's Toxicologic Emergencies - 8th Ed. (2006)

4 Stages of Toxicity

- Stage 1: Preclinical
 - Hepatic injury yet to occur
 - Normal AST/ALT
 - Nausea, vomiting, diaphoresis, pallor, lethargy and malaise
- Stage 2: Hepatic injury
 - Within 24 hours of ingestion
 - Increased AST
 - Prolonged PT, elevated bilirubin, metabolic acidosis
 - May have temporary symptomatic improvement

Hendrickson R et al. in: Goldfrank's Toxicologic Emergencies - 8th Ed. (2006)

4 stages of toxicity

- Stage 3: Fulminant Hepatic Failure
 - 72 - 96 hrs. after ingestion
 - AST / ALT > 10,000 IU/L are common
 - Abnormal PT, bilirubin, phosphate, pH, and lactate
 - Encephalopathy, coagulation defects, or coma
 - Fatalities generally 3 - 5 days after acute overdose
 - Multiorgan failure, ARDS, sepsis, cerebral edema
- Stage 4: Recovery
 - Hepatic regeneration
 - Resolution of symptoms and normalization of laboratory values may take several weeks
 - Histologic abnormalities may persist for months

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Risk of Toxicity

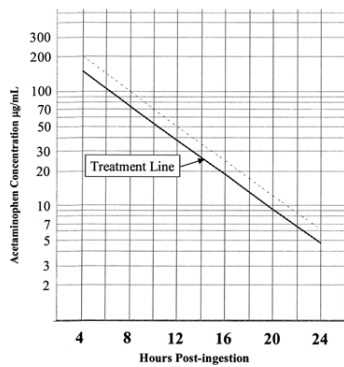
- Majority of APAP exposures result in no toxicity
- Acute vs. Chronic
- Acute overdose (over a 4 hour period):
 - 150 mg/kg in pediatrics
 - 7.5 grams in adults (15 grams?)
- Dose estimates may not be reliable in patients with attempted self-harm

Hendrickson R et al. in: Goldfrank's Toxicologic Emergencies - 8th Ed. (2006)

Risk of Toxicity

- Determination of APAP concentration
 - Rumack Matthew nomogram
 - Line was developed based on aminotransferase conc.
 - Starts at 4 hrs post-ingestion (complete absorption)
 - Extended release formulations?

Acetaminophen Nomogram



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Chronic Overdose Exposure

- Max daily dose = 4000 mg or 90 mg/kg in children
- Risk for serious toxicity after repeated therapeutic doses is negligible
- Insidious onset of symptoms and failure to ask specifically about APAP use
- APAP blood levels are frequently normal
 - Patient presents late in the course of the disease

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Influencing Factors

- Excessive intake
- Chronic alcoholism
 - Induction of CYP2E1
- CYP2E1 inducers
 - Rifampin, phenobarbital
- Competition for glucuronidation
 - SMX/TMP, Zidovudine
- Malnutrition
 - Depletion of GSH

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Chronic Overdose Exposure

- Risk for toxicity if:
 - Signs / symptoms of hepatotoxicity
 - AST > 2 times normal
 - AST elevated and patient symptomatic or APAP conc > 10 mcg/mL
 - APAP conc is higher than expected
 - Elevated PT
 - Concomitant acute renal failure

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Treatment

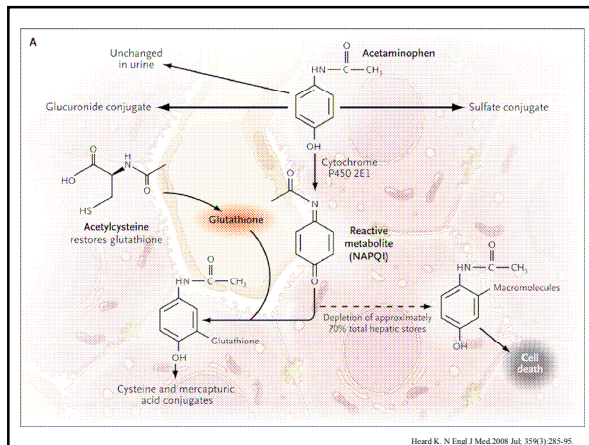
- Activated charcoal reduces APAP absorption by 50 to 90%
- Single dose of 1 g/kg
- Activated charcoal also adsorbs NAC and, by causing nausea and vomiting, may interfere with the administration of NAC

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N-Acetylcysteine (NAC)

- 1st suggested as an antidote in 1974
- Serves as GSH precursor
 - Can also serve as a GSH substitute
- Has been shown to reduce mortality in patients with acetaminophen-induced hepatic failure.
- Prevents toxicity by limiting formation of NAPQI
- Increases the capacity to detoxify formed NAPQI
- Acts through nonspecific mechanisms that preserve multiorgan function

Heard K. N Engl J Med. 2008 Jul; 359(3):285-95



Heard K. N Engl J Med. 2008 Jul; 359(3):285-95

N-Acetylcysteine (NAC)

- Efficacy is nearly complete as long as administered within 8 hrs of ingestion
 - Efficacy decreases with time
- Benefit still observed if treatment delayed
- Demonstrated to diminish the need for vasopressors and incidence of cerebral edema after fulminant hepatic failure

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IV vs. PO NAC

	IV	PO
Dose	150 mg/kg x 1 over 60 min then 50 mg over x 1 over 4 hrs then 100 mg/kg over over 16 hrs	140 mg/kg x 1 then 70 mg/kg q 4 hrs x 17 doses <i>Total of 72 hours</i>
Other Notes	Anaphylactoid reaction (17%) Potential dosing errors Infusion of large fluid volumes More expensive drug cost	Difficult to use if vomiting or altered mental status Longer duration of therapy More monitoring (nursing costs) Not studied in fulminant hepatic failure

Duration of NAC

- Therapy should be continued at end of protocol if evidence of significant liver injury:
 - AST greater than normal or .
 - APAP conc. > 10 mcg/mL
- Decision to DC NAC should be based on patient condition
 - If liver failure, then continue IV NAC until PT is near normal and encephalopathy, if present, has resolved
 - If no liver failure, but elevated AST, continue NAC until AST normalizes

Hendrickson R et al, in: Goldfrank's Toxicologic Emergencies - 8th Ed (2006)

Summary

- Hepatotoxicity from acetaminophen overdose due to NAPQI metabolite
- Toxicity can be from acute or chronic exposure
- Timing of levels is important for determining relative toxicity
- NAC acts as a glutathione precursor
- Decision to use IV or PO NAC is multifactorial

Toxic Alcohols



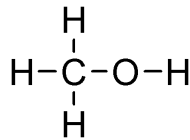
Toxic Alcohols

- Alcohols are hydrocarbons that contain a hydroxyl group
- Commonly refers to methanol, ethylene glycol, and isopropanol
 - Alcohols not intended for ingestion
- Other less common but potentially toxic alcohols include:
 - Diethylene glycol, benzyl alcohol, and glycol ethers

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Methanol

- Colorless, odorless, bitter-tasting, highly volatile
- Used in embalming fluid in ancient Egypt
- Window washer fluid
- Photocopying fluid
- Perfumes
- Solvent
- Varnish and paint removers



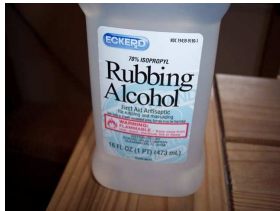
Ethylene Glycol

- Odorless, sweet tasting
- Engine coolant during WWII
- Antifreeze
- Brake fluid



Isopropanol

- Colorless, bitter-tasting, smells like acetone
- Most common reported toxic alcohol exposure reported
- Rubbing alcohol
- Glass cleaner
- Aftershave
- Skin lotions



Toxicokinetics

- Exposure via skin or inhalation possible
- Readily absorbed after ingestion
- Not completely bioavailable
 - Gastric alcohol dehydrogenase, 1st pass metab.
- Time to peak concentration
 - Ethylene glycol: 1-4 hrs
 - Methanol, isopropanol: 30-60 min

Toxicokinetics

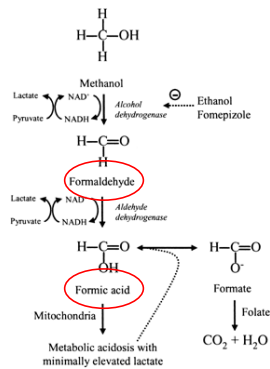
- Eliminated primarily through metabolism by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)
- Enzyme binding affinities
 - Ethanol > methanol > ethylene glycol
- Metabolism follows zero-order kinetics

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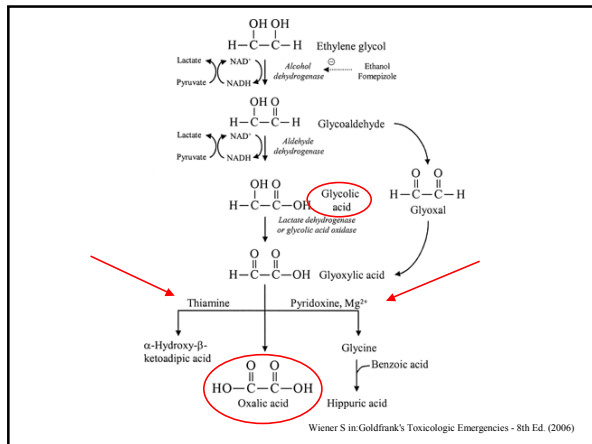
Toxicokinetics

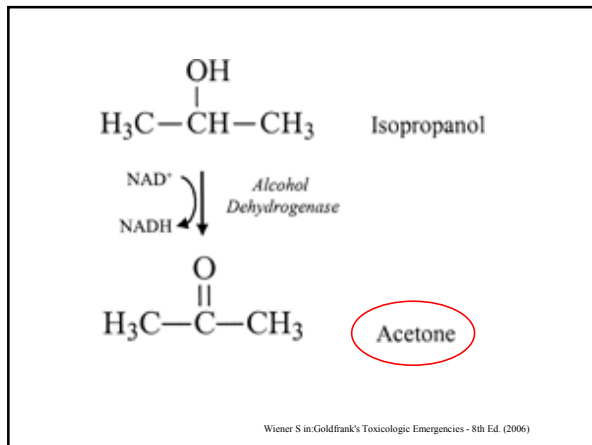
- Alternate metabolic pathways exist
 - Targets for potential therapy
- Methanol and ethylene glycol may be excreted unchanged
 - Methanol □ pulmonary excretion
 - $t_{1/2}$ 30-54 hrs
 - Ethylene glycol □ renal excretion
 - $t_{1/2}$ ~ 8.5 hrs

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Clinical Manifestations

- Inebriation
- Higher molecular weight alcohols more intoxicating
 - Isopropanol ~ ethylene glycol > ethanol > methanol
- Inebriation may be absent
 - Chronic drinkers
- Ataxia, dizziness, convulsions, hypothermia

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Clinical Manifestations

- Anion gap metabolic acidosis
 - Methanol and ethylene glycol
- Consequence of metabolism to toxic organic acids
 - Formic acid, glycolic acid
 - No rapid natural metabolic pathway
- Not seen with isopropanol
 - Do see ketosis without acidosis

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Specific End-Organ Effects

- Methanol
 - Visual impairment snowfield
 - Correlated to severity of metabolic acidosis
- Ethylene glycol
 - Nephrotoxicity due to oxalic acid complexing with calcium
- Isopropanol
 - Hemorrhagic gastritis large ingestion

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Diagnosis

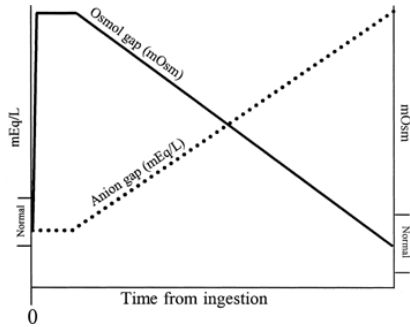
- Serum levels ideal but not always available
- > 25 mg/dL considered toxic for methanol and ethylene glycol
- Surrogate markers
 - Calcium, BUN, SCr, UA, serum ethanol

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Diagnosis

- Anion gap acidosis
 - May take up to 24 hrs with methanol
- Osmolar gap
 - = Measured SOsm calculated SOsm
 - Neither sensitive nor specific
 - Inversely proportional to anion gap
 - Accumulation of alcohols will raise measured serum Osm

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Management

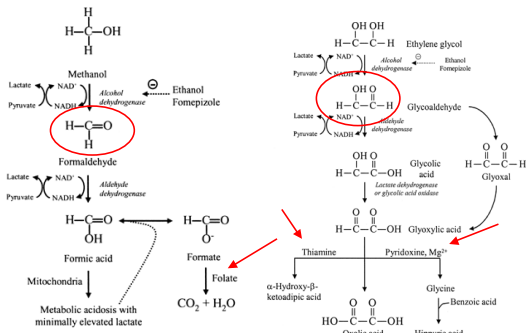
- ABCs
- Fluid resuscitation
- NG tube aspiration
- GI decontamination with lavage not useful
- Sodium bicarbonate

Kraut J et al. Clin J Am Soc Nephrol. 2008 Jan;3(1):208-25.

Management

- Thiamine and pyridoxine in ethylene glycol toxicity
- Folic acid in methanol toxicity
- Hemodialysis
- Inhibition of ADH
 - Needs to be initiated while sufficient alcohol remains unmetabolized

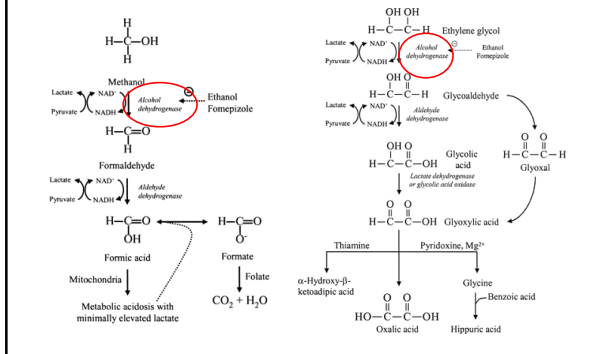
ADH Inhibition



ADH Inhibition

- | | |
|--|--|
| <input type="checkbox"/> Ethanol | <input type="checkbox"/> Fomepizole |
| <input type="checkbox"/> PO or IV | <input type="checkbox"/> IV or PO? |
| <input type="checkbox"/> Frequent levels | <input type="checkbox"/> No CNS depression |
| <input type="checkbox"/> Difficult titration | <input type="checkbox"/> Easy dosing |
| <input type="checkbox"/> CNS depression | <input type="checkbox"/> 500-1000 x \bar{s} greater affinity for ADH than EtOH |
| <input type="checkbox"/> Hypoglycemia | <input type="checkbox"/> No levels to monitor |
| <input type="checkbox"/> Hypotension | <input type="checkbox"/> No hypoglycemia |
| | <input type="checkbox"/> \$\$\$ |

ADH Inhibition



Fomepizole

- Competitive antagonist of ADH
 - Higher affinity than EtOH
- Dose
 - LD = 15 mg/kg x 1, then
 - 10 mg/kg q 12 hrs for 4 doses, then
 - 15 mg/kg q 12 hrs until patient asymptomatic with normal pH
- Can be used in combination with dialysis
- Can cause nausea, headache, dizziness

Summary

- Ethylene glycol toxicity associated with renal failure
- Methanol toxicity associated with visual disturbances
- May have lag in symptom onset with methanol ingestion due to slower metabolism
- Ketosis without acidosis = isopropanol
- Fomepizole acts on alcohol dehydrogenase inhibiting the formation the toxic metabolites of toxic alcohols

The End
