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.
Pharmacists 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

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**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

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**Atropine**
- 0.01-0.02 mg/kg IV push
- May prevent bradydysrhythmia
  - 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
**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

**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

**Sedative Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Onset / Duration</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>0.3 mg/kg IV</td>
<td>35 sec / 5-1 min</td>
<td>Pharmacodynamic stable; Decrease ICP &amp; IOP</td>
<td>Adrenocortical suppression; Myoclonus, pain on injection</td>
</tr>
<tr>
<td>Thiopental</td>
<td>2.5 mg/kg IV</td>
<td>30-60 sec / 0-1 min</td>
<td>Pharmacodynamic stable; Decrease ICP &amp; IOP</td>
<td>Hypotension; Histamine release</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1-2 mg/kg IV</td>
<td>30-60 sec / 0-1 min</td>
<td>Pharmacodynamic stable; Analgesic / amnestic</td>
<td>Increased sympathetic outflow; Emergence phenomena</td>
</tr>
<tr>
<td>Propofol</td>
<td>1-2.5 mg/kg IV</td>
<td>30 sec / 5-10 min</td>
<td>Decreased ICP &amp; IOP; Amnestic</td>
<td>Depression of laryngeal &amp; pharyngeal reflexes; Dose-related hypotension</td>
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</table>
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

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.

Succinylcholine

- Bradydysrhythmia
  - Pediatric patients and after repeat dose in adults
  - Atropine may mitigate
- Increased IOP and ICP
  - Transient
  - Fasciculations
Non-Depolarizing NMB\'s

- Competitively bind to Ach receptors preventing muscular depolarization
- Rocuronium:
  - Dose: 0.6 - 1 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.


<table>
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<th>Paralytic Agents</th>
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<tbody>
<tr>
<td>Agent</td>
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<tr>
<td>Sux</td>
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<td></td>
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<tr>
<td>Rocuronium</td>
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<tr>
<td>Vecuronium</td>
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</tbody>
</table>

Postintubation Management

- Sedation
  - Continuous infusion of sedative agent
  - Titrate to desired effect
- Paralytic
  - Does not provide any analgesia or sedation
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
  - Chorpheniramine
  - 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.
NAPQI
- Extremely hepatotoxic
- Rapidly detoxified with glutathione (GSH)
- Acetaminophen overdoses can deplete GSH supply

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

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

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

- **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
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?

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
Influencing Factors

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

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

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
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


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

IV vs. PO NAC

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

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

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.


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.

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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

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

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

Specific End-Organ Effects

- Methanol
  - Visual impairment
  - Correlated to severity of metabolic acidosis

- Ethylene glycol
  - Nephrotoxicity due to oxalic acid complexing with calcium

- Isopropanol
  - Hemorrhagic gastritis
    - Large ingestion

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
Diagnosis

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

Management

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

- Ethanol
  - PO or IV
  - Frequent levels
  - Difficult titration
  - CNS depression
  - Hypoglycemia
  - Hypotension
- Fomepizole
  - IV or PO?
  - No CNS depression
  - Easy dosing
  - 500-1000 x greater affinity for ADH than EtOH
  - No levels to monitor
  - No hypoglycemia
  - $$$

ADH Inhibition

- 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

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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 of toxic metabolites of toxic alcohols
The End