Clinical Summary

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TCA Overdose

Understand the pathophysiology of tricyclic antidepressants (TCAs)

- TCAs are "dirty" drugs—they have effects on multiple cellular levels
- Blockade of cardiac fast acting sodium channels
  - Causes prolonged QT, conduction delay, decreased inotropy
- Antagonism of central and peripheral muscarinic acetylcholine receptors
  - Results in "anticholinergic toxidrome"—blind as a bat, mad as a hatter, red as a beat, hot as a hare, dry as a bone, etc.
- Antagonism of peripheral alpha 1 receptors
  - Results in peripheral vasodilation and hypotension
- Antagonism of GABA receptors
  - Causes seizures
- Antagonism of histamine receptors
  - Sedation
- Variable in terms of half-life, can range from 7 hours to 42 hours

Understand the clinical features of TCA toxicity

- Cardiovascular
  - Sinus tachycardia—secondary to anticholinergic effects
  - Hypotension –from alpha adrenergic antagonism as well as cardiac conduction issues
  - VT and VF are uncommon (<5%)
  - EKG changes including prolonged QT >100. In one study patients with QRS >100 had a 26% chance of seizure, and those with QRS >160 had 50% chance of ventricular arrythmia
- CNS
  - Somnolence (from antihistaminergic)
  - Seizures (from anti-GABA)
- Anticholinergic
  - Flushed skin, dilated pupils, delirium, hyperthermia, urinary retention

Appreciate the options for enhanced elimination of TCAs (activated charcoal, whole bowel irrigation, gastric lavage)

- Charcoal- expert recommendation is 1g/kg up to 2 hours after ingestion. Of course, ONLY if alert and no risk of airway compromise. Otherwise, intubate first, then provide this
- No role for WBI or gastric lavage

Identify and understand first-line treatment options for symptomatic TCA poisoning, particularly the role of sodium bicarbonate

1. Cardiac Abnormalities (increased QRS, hypotension, poor contractility)
   - Sodium bicarbonate
     - This will improve the QRS as well as improve hypotension (think of it as a vasopressor)
     - Target is narrowing of the QRS (goal < 100ms)
     - Suggested starting dose is 1-2 meq/kg bolus. Generally, this will be about 1-2 amps of sodium bicarbonate, IV push
     - If no improvement after the first dose, can repeat in 5 minutes
     - If improvement with bicarb, start an infusion
     - In the case of none, or little improvement in hemodynamics and QRS with the sodium bicarbonate, it is still recommended to start an infusion
     - Arterial line placement is recommended as frequent ABG's will be required to TARGET A PH of 7.5 – 7.55.
       - **ABG should be measured hourly, in addition to electrolytes as SEVERE hypokalemia, hypernatremia could result from this**
     - 80-90% of cases will respond to this treatment (there will be decrease QRS and resolution of hypotension)
     - Sodium bicarbonate infusion is recommended as well (3 amps in 1 L D5) at 250 cc/hr in adult patients OR twice the maintenance infusion rate
   - Vasopressors
     - Should sodium bicarb not provide adequate improvement in hemodynamic response, vasopressors can be used (see below)
   - Fluid
     - Recommended to provide NS boluses

2. CNS dysfunction (somnolence, seizures)
   - Intubation- if required
   - Benzodiazepines
     - Recommended in those with seizure activity
     - Phenytoin not recommended as mechanism of action does not result in decreased seizures with TCA toxicity (it works on sodium channels)
     - In general, NEVER give phenytoin in tox-related seizures
     - Phenobarbital recommended if secondary drug required

3. Anticholinergic
   - Place foley catheter to avoid urinary retention
   - Sodium bicarbonate will improve the remaining symptoms
   - Cooling

Recognize treatment options for refractory toxicity including vasopressors, magnesium, hypertonic saline, and intralipid therapy

- Vasopressors

    - Use only if inadequate response to sodium bicarbonate boluses and infusion as well as NS fluid boluses
    - Due to anti-alpha effects, norepinephrine or phenylephrine are excellent choices
- Magnesium
    - Can provide if arrythmia (prolonged QRS) is unresponsive to sodium bicarb
    - One RCT does demonstrate some mortality improvement if 1-2 g IV Mg is provided in addition to sodium bicarb
- Hypertonic saline
    - No evidence, but can use after adequate alkalinization is achieved and patient is still unstable
    - Ensure patient's serum sodium is checked prior to administration
- Lidocaine
    - 1 mg/kg IV bolus then infusion at 20-30 mcg/kg/min
- Intralipid
    - No clear indications, but can be used
    - Suggested to use in prolonged cardiac arrest or in extremely refractory cases
    - Use in combined decision with toxicologist

Organophosphate Poisoning

Understand the pathophysiology of organophosphates

- Often found in pesticides and insecticides
- Lipid-soluble and non-lipid soluble. Non-lipid soluble are FAST acting and typically cause moderate to severe symptoms quickly (within 3 hours)
- Organophosphates inhibit acetylcholinesterase (AChE) which causes accumulation of acetylcholine and overstimulation of the receptors in the autonomic nervous system, and CNS.

Understand the toxidrome of organophosphate poisoning

- SLUDGE and the Killer B's is most common
    - Salivation, Lacrimation, Urination, Defecation, Gastric Emesis, Bronchorrhea, Bronchospasm, Bradycardia
        - Fluid leaking from every hole – top to bottom
            - Eyes (lacrimation)
            - Mouth (salivation)
            - Opening to esophagus (emesis)
            - Opening to airway/larynx (bronchorrhea)
            - Urethra (urination)
            - Rectum (defecation).
- The above are primarily symptoms of parasympathetic NS stimulation from acetylcholine
- They can also cause fasciculations, weakness, as well as seizures, and decreased GCS. These are uncommon (these are from acetylcholine activation of somatic neurons and CNS neurons)
- Cardiac issues including QT prolongation, VT, and cardiomyopathy are possible but not common in organophosphate poisoning
- Respiratory issues are the MOST COMMON CAUSE OF FATALITY in these cases. This is due to combination of CNS respiratory depression as well as bronchoconstriction, bronchorrhea**.**

Recognize the need for patient decontamination and importance of adequate healthcare provider PPE

- Aggressive decontamination should be provided in cases where tremendously potent compounds are the cause of the poisoning (i.e. compounds with toxic dermal absorption)
- In all cases, it is advised to remove the patient's clothes and irrigate with soap and water if possible
- PPE include facemask, googles, gown is advised

Appreciate the options for enhanced elimination of organophosphates (activated charcoal, whole bowel irrigation, gastric lavage)

- Charcoal shows no benefit after 1 hour
- Gastric lavage not recommended as very limited evidence and possible risk of harm through aspiration
- WBI not indicated

Identify and understand first line treatments for symptomatic organophosphate poisoning, particularly the role of atropine, epinephrine and pralidoxime

- Atropine
    - Competes with acetylcholine at the muscarinic receptors (but not nicotinic)
    - Beginning dose of 2-5 mg IV, IM or IO
    - Double the dose q5 minutes
    - Sometimes, HUNDREDS OF MILIGRAMS ARE NEEDED
    - Infusion is 10-20 % of dose required to alleviate symptoms every hour
    - Mydriasis and tachycardia may occur but this is NOT a reason to stop atropine→ target is reduction/resolution of respiratory symptoms (drying of respiratory secretions)
    - If hospital runs out of atropine, can consider glycopyrrolate, which will help with the respiratory secretions but it won't cross the BBB and there wouldn't be an CNS improvement from this.
- Pralidoxime
    - Pralidoxime regenerates phosphorylated acetylcholinesterase and prevents 'aging' (irreversible binding of the organophosphate to AchE)
    - Because it binds to acetylcholinesterase it MUST be given after atropine as it could make the symptoms worse (could precipitate more cholinergic symptoms)
    - Dose is 2 g IV over 30 minutes, followed by an infusion at 8 mg/kg/hr (Max dose of 650mg/hr. Alternatively, you could run the infusion at 500mg/hr).
    - Rapid infusion can result in temporary worsening of cholinergic manifestations (tachycardia, laryngospasm, muscle rigidity and cardiac arrest)
    - Evidence is scarce with several RCT demonstrating differing outcomes, but for now expert recommendation is to use this

- Epinephrine
    - If atropine is not resulting in HR 80, consider epinephrine infusion starting at 5-10 mcg/min
    - Target HR is generally considered to be HR > 80
    - Most patients only need this for 12-24 hours

Understand the importance of early airway management in patients with organophosphate poisoning

- Most patients with any airway secretions, bronchospasm need to be intubated eventually. It is better to do this upon patient arrival before secretions worsen, making intubation more difficult
- Re bronchospasm→ Inhaled beta agonists (Ventolin) are NOT shown to be effective

Recognize that high doses of atropine may be required to resuscitate a patient with organophosphate poisoning

Identify treatment targets for patients with organophosphate poisoning

- Therapeutic endpoint is primarily targeted with atropine. Target should be clearing of respiratory secretions and cessation of bronchoconstriction. Tachycardia and mydriasis should NOT be used as endpoints and are NOT contraindications for continuing atropine. Mydriasis often occurs after the initial doses of atropine however should not be used as a sign of effective treatment.

Additional Points:

- Rocuronium is preferred over sux. If you do use sux then the duration of effect/half-life of sux will be significantly prolonged because sux is hydrolyzed by plasma cholinesterase (aka pseudocholinesterase).

- Reasons to switch from atropine to another anticholinergic:
    1. Severe CNS manifestations of ANTI-cholinergic toxicity.
    2. Run out of atropine.

- Agent to switch to (instead of atropine):
    1. Glycopyrrolate (as this does not cross the BBB into the CNS).
    2. Diphenhydramine (Benadryl).