CONTROVERSIES SURROUNDING COMMON ANTIDOTES: ACETYLCYSTEINE AND PHYSOSTIGMINE

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Objectives

Recognize the differences between IV and Oral acetylcysteine treatment in the treatment of acetaminophen toxicity
Recognize when the use of physostigmine is indicated and contraindicated

Acetylcysteine and Physostigmine

- N-Acetylcysteine (NAC)
  - Glutathione regenerant

- Physostigmine (PSG)
  - Acetylcholine Esterase Inhibitor
**N-Acetylcysteine (NAC) IV/Oral**

- The Antidote for Acetaminophen toxicity
- Expanded role for glutathione-depleted hepatocellular Injury
  - Chlorinated solvents
  - Pennyroyal
- Radiocontrast-induced renal insufficiency/ failure
- Routes of Adminstration – IV, ORAL

**N-Acetylcysteine (NAC) IV/Oral**

- NAC is a thiol compounds that deacetylates to cysteine
- Cysteine + Glycine + Glutamate
  - Glutathione
  - $\text{ACTM} \rightarrow \text{NAPQI}$ (toxic radical)
  - NAPQI + Glutathione $\rightarrow$ APAP

**N-Acetylcysteine (NAC) IV/Oral**

- Oral Protocol
  - 140 mg/kg Load; 70 mg/kg every 4 hrs; 72 hours
  - Pt compliance – intoxicated, vomiting, angry
  - Concommitant Activated Charcoal – reduced absorption
  - Primary Adverse Effect was vomiting – hard to detect from ACTM OD itself
  - Swamp Gas odor
N-Acetylcysteine (NAC) IV/Oral

- IV Protocols
  - Inhalational converted to IV use without difficulty for Pediatric and Adult Patients
  - 140/mg/kg; 70 mg/kg Every 4hours;
  - 20 HR 48HR (36 and 72 )
  - In 2010 FDA Approved 20 hr IV Acetadote™
    • 150 mg/kg in 60 min; 50 mg/kg in 4hr; 100 mg/kg in 16 hrs – wt based diluent (<20 kg; 20-40 kg; >40 kg)

N-Acetylcysteine (NAC) IV/Oral

- IV NAC Protocols – Adverse Events
  - Anaphylactoid/Anaphylactic
    • Hives, wheezing, nausea, vomiting
  - Dougherty, TD., et al., Abstract NAACT conf, 2002
    • Comparison of 48 hr IV Continuous v Batch Dose; Anaphylactoid reactions controlled with pretreatment and duration of infusion
  - Increased INR - Wasserman, GS., Pediatr Primary Care, 2003; 17:4

N-Acetylcysteine (NAC) IV/Oral

N-Acetylcysteine (NAC) IV/Oral

- Yarema, MC., et al
  - Retrospective Study, 2 Large Cohorts of 4048 Pts
  - Oral 1962 (US)
  - IV 2086 (Canadian)
  - Surrogate measure of hepatotoxicity (ALT/AST >1000)
  - IV NAC Outcomes better if post-ingestion was treatment ≤12 hrs
  - Oral NAC Outcomes better if post-ingestion treatment after 18hrs
  - Unclear if 12 to 18 hrs post ingestion
N-Acetyl cysteine (NAC) – IV/Oral

Yarema, MC., et al, 2009

Problems with the study included:

- Ethanol exposure was larger in the IV NAC
  - Yarema, MC, Ann Emerg Med 2005: that quantified risk with IV NAC; “Ethanol has variable effects”
  - Total doses (mg/kg) iv:300 oral:1330
  - Surrogate outcome measure “hepatotoxicity” v death/ transplant
  - AST/ALT v Kings College Criteria with PO4, lactate

N-Acetyl cysteine (NAC) – IV/Oral

Yarema, MC., et al

Problems with the study included:

- Bond, GR., Editorial, Ann Emerg Med, 2009; Dec
  - Late presentation and confounding middle period hepatic injury in orally tx pts – late presenter and high dose exposure may benefit from prolonged therapy
  - ACTM overdose kinetics make 4-hour extrapolation of the data less reliable
  - Chronic/Acute alcohol effects on P-450 metabolism
  - Most treated patients do well but high exposure ACTM may need prolonged or accentuated NAC dosing

N-Acetyl cysteine (NAC) – IV/Oral

Safety of IV v Oral

  - 503 Pts - 306 iv, 197 oral, 52 both
  - Nausea/Vomiting more common in Oral
  - Anaphylactoid more common in IV
  - No significant adverse events in all groups
N-Acetylcysteine (NAC) – IV/Oral

- NAC for Preventing non-iodine radiocontrast Nephropathy
  - Percutaneous coronary interventions; sometimes mixed with NaHCO3 it also did not prevent dialysis
  - 600 mg IV doses have not shown reduction in renal injury
  - Oral dose not shown effective and suggested higher IV doses hint at incurred adverse events

N-Acetylcysteine (NAC) – IV/Oral

- Economic Issues
  - Martello, JL., et al., “Cost minimization analysis comparing enteral N-acetylcysteine to intravenous acetylcysteine in the management of acute acetaminophen toxicity” Clin Toxicol (Phila); 2010; Jan; 48(1):80-86
  - 261 Pts Retrospective cohort
  - 70 Oral, 191 IV
  - Costs associated with Oral $18,200 IV $7600
  - LOS – median (days)
    - Oral 7 (5-13)
    - IV 4 (3-6)

N-Acetylcysteine (NAC) – IV/Oral

- Economic Issues
  - Discussion
    - IV therapy inherently shorter regardless of outcome
    - LOS is what drives the cost and decreasing LOS is the CMS gold-standard
  - Cape Coral Hospital
    - $25 oral NAC – non-proprietary
    - $550 IV NAC - non-proprietary
    - $400 IV NAC – Acetadote
    - -source Troy Pinta, PhD
N-Acetylcysteine (NAC) – IV/Oral

- Discussion
  - Oral or IV are both suitable Methods
  - Oral requires Pt compliance to be effective; Portal circulation is potential advantage?
  - IV NAC requires more vigilance for adverse events but both oral and IV have mild adverse effects
  - Pediatrics not addressed
  - Economic issues driven by LOS
  - Patient-tailored therapy may be best:
    - High dose exposure
    - Late presentation
    - Acute and/or chronic Alcohol use

Physostigmine (PSG)

- Background
  - Derived from the calabar bean plant
  - Acetylcholinesterase inhibitor that crosses the blood brain barrier (as opposed to neostigmine)
  - Anti-Muscarinic
  - Used to treat glaucoma, myasthenia, as a reversal for pharmacological induced paralysis (curare), and as an antidote to atropine
  - Diagnostic and therapeutic with regard its use in anticholinergic “poisoning”
    - Over 600 agents respond to its effect

Physostigmine (PSG)

- Background:
  - Death from anti-cholinergic toxidrome is rare, and therefore its use to “cure” this non-lethal syndrome comes under scrutiny
  - Deaths from its use in TCA overdoses
  - Enhanced vagal activity
  - Intensified depressant cardiac conduction and cardiac output effects already inherent with TCA toxicity
  - Physostigmine and Tricyclic Anti-Depressants (TCAs)
    - [position statement]
      - The use of PSG for therapeutic anti-cholinergic treatment of TCA poisoning can result in death
      - PSG is not indicated in any intoxication that cannot be fully attributed to an antimuscarinic agent
Physostigmine (PSG)

- Literature Review
  - Recommendation for the use of PSG in TCA overdose in the PDR
  - Of 20 entries, 3 (15%) had contraindicated treatment recommended

Physostigmine (PSG)

- Literature Review
  - Retrospective case control, 52 pts, University setting

- CNS agitation score developed for amphetamines – Table 1

<table>
<thead>
<tr>
<th>Severity Score</th>
<th>Clinical Findings</th>
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<tbody>
<tr>
<td>0</td>
<td>Relaxed, cooperation</td>
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<tr>
<td>1</td>
<td>Anxiety, irritability, tremor</td>
</tr>
<tr>
<td>2</td>
<td>Unsteady or mildly disoriented, confused, and disorienting, moderate agitation and motor incoherency</td>
</tr>
<tr>
<td>3</td>
<td>Hyperactive agitation, flighty</td>
</tr>
<tr>
<td>4</td>
<td>Seizures, deep coma, incoherence to voice or pain</td>
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Physostigmine (PSG)

- Literature Review (Burns 1999)
- Conclusions:
  - PSG used as 1st line therapy; ECG QRS duration used for exclusion
  - PSG more effective in reducing agitation, with Benzo's having tendency to increase LOS
- Limitations
  - Small study
  - Benzodiazipine arm very small in Sole agent

Physostigmine (PSG)

- Literature Review
  - Included in PSG Antidote Chapter on Goldfrank’s Toxicology
  - 3 cases of recreational intoxication
  - PSG given: 2 mg, 3mg, 0.5 mg x 3 Q5 min (1.5 mg)
  - "Comprehensive" urine drug screens done; no mention of TCA and whether screen before or after PSG
  - Discussion also reports another case not responsive
  - Attempt to diminish concern for PSG induced Sz in unrecognized TCA overdose
Physostigmine (PSG)

• Literature Review
  • PSG use in TCA cases
    • Newton 2 pts with seizures (2 mg in 2 min)
    • Walker 3 pts with seizures (2 mg in 2 min)
    • Pentel & Peterson (1980s)
      • 2300 mg amitriptyline – seizure, asystole and survived
      • 5000 mg imipramine – seizure, asystole, death
      • Both pts with significant TCA toxicity

Physostigmine (PSG)

• Literature
  • PSG use in TCA cases as it relates to QRS duration
    • Case of Amtriptiline and Trifluoperazine, QRS >100 ms
    • 1 mg dose and asystole, resuscitated; 1 mg again with asystole and died 2 days later
    • 43 pts maprotiline overdose
    • 62 pts with PSG pts had seizures
    • Seizure increased with QRS >100ms
    • PSG in Burn article may have selected out
    • Amtriptiline in dogs

Physostigmine (PSG)

• Literature
  • QRS >100 ms in Burn article may have selected out sicker TCA cases
  • Amtriptiline in dogs
  • NaHCO3 most efficacious
  • PSG next best agent to narrow QRS
Physostigmine (PSG)

- Literature
  - PSG use in TCA cases
    - PSG reported to improve cardiotoxicity (shorten QRS), however prolonged QRS indicative of more severe TCA toxicity and therefore likely to worsen neurotoxicity and result in seizures which do worsen cardiac and neurologic consequences
    - PSG went from 1st-line agent to contraindicated based on 1980s 2 cases, to case specific selection

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Physostigmine (PSG)

- Literature Review
  - Assertion that benzodiazepines are less effective than PSG
  - "Judicious use" of PSG for life-threatening effects, esp in pediatrics
  - PSG’s half-life significantly shorter than Belladonna but continuous infusion not warranted
  - Duration of action 1-2 hrs
  - Elimination t1/2 15-40 min (atropine 2-3 hrs)

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Physostigmine (PSG)

- Literature Review
  - 8 yrs of of APCC botanical exposures; 30 deaths, 5 from Datura sp.
  - Treatment Dose
    - Adult: 1 mg/min, 3rd dose in 20 min for additional response
    - Peds: 0.02 mg/kg, rate not to exceed 0.5 mg/min
Physostigmine (PSG)

- Literature Review
  - Response to Krenzelok
  - 85 patients treated with PSG without any adverse effects
  - 49 pts, age 11-28, also treated with repeated doses, avoiding the need for other medications (benzodiazepines) and a longer LOS
  - More positive approach to PSG

  - Retrospective chart review and descriptive case series
  - 41 pts received PSG in ED, 4 in ICU
  - 41 (73%) single dose, 14 (31%) multiple doses (5 were discharged);
  - max time between doses 6.5 hrs
  - 19 (46%) discharged; 14 (35%) floor; 12(29%) ICU
  - Most multi-doses to floor 6 (43%)
  - ECG findings QRS max 106 ms; QTc max 558 ms
  - No seizure or arrhythmia reported
  - Mean LOS (days)
  - Single dose 2.6
  - Multiple 5.4

- Discussion
  - What to do?
    - PSG appears to be effective and safe in pure antimuscarinic intoxication
    - Identification of obscure TCA intoxication can be difficult
    - PSG use in anti-muscarinic cases can result in unpredictable seizure in known and obscured TCA toxicity and result in death
    - Use of PSG for "pure" anti-muscarinic treatment remains at the discretion of the risk-neutral clinician
Post Course Review of NAC and PSG

T/F?

- There is clear consensus for IV NAC over Oral NAC
- Ethanol abuse is easily accounted for as a confounding variable in NAC therapy
- Economic considerations are paramount when considering IV v Oral NAC
- Benzodiazepines show similar benefit to PSG in the treatment of anti-muscarinic toxicity
- Multiple-dose PSG portends an ICU admission
- Exclusion criteria for PSG in TCA overdose generally prevents adverse effects