A NAC for Toxicology: Just Add Fat, Salt, and Spice

Heather M. Draper, Pharm.D., BCPS
Clinical Pharmacist, Emergency Medicine
Mercy Health Saint Mary’s
February 13, 2014
Disclaimer

I have no real or perceived conflicts of interest related to the content of this presentation.
Objectives

• Compare and contrast the use of oral and intravenous regimens of N-acetylcysteine for the treatment of acetaminophen toxicity.

• Identify the clinical utility of intravenous lipid emulsion for the treatment of drug toxicity.

• Describe the anticipated clinical presentation and effects associated with ingestion of: *Salvia*, Kratom, and Krokodil.
A NAC for Toxicology: N-Acetylcysteine for Acetaminophen Poisoning

(NAC: Not Always Clear cut)
Acetaminophen Toxicity

- Acetaminophen metabolized to N-acetyl-p-benzoquinone imine (NAPQI)
  - Detoxified by glutathione

- In overdose, glutathione stores are depleted and nontoxic metabolism is saturated, leading to increased NAPQI

- NAPQI is directly hepatotoxic
Acetaminophen Toxicity

• Reported mortality rate: 0.5%

• Leading cause of liver transplant in United States (U.S.) and most of Europe

• Acute overdose threshold: 150 mg/kg

• Chronic overdose: repeated supratherapeutic ingestion
Acetaminophen Toxicity

- Stage I: generally asymptomatic; nausea, vomiting, malaise, diaphoresis may occur

- Stage II: onset of acute liver injury

- Stage III: maximum hepatotoxicity, fulminant liver failure

- Stage IV: recovery phase
The Rumack-Matthew Nomogram

- Rumack-Matthew used to risk stratify acute acetaminophen exposures
- Nomogram “starts” at 4 hours post-ingestion
Acetaminophen Toxicity: 
N-Acetylcysteine as an Antidote

• N-acetylcysteine (NAC) serves several roles in acute acetaminophen toxicity
  – Serves as glutathione precursor
  – Increases nontoxic sulfonation
  – May reverse NAPQI oxidation
  – May diminish hepatocyte injury

• NAC may preserve cerebral perfusion and reduce renal toxicity
N-Acetylcysteine: Which Way Does It Go?

• Great “debate” – perception – regarding intravenous versus oral route of administration

• Intravenous (IV) and oral (PO) regimens are equally efficacious

• *Still* no head-to-head comparison of IV versus PO regimens…

Goldfrank’s Toxicologic Emergencies, 9th ed.
Intravenous versus Oral N-Acetylcysteine

- Direct delivery into portal circulation with PO NAC results in high(er) liver concentration
  - 20- to 30-fold lower serum concentration than IV route
  - May be advantageous when given soon after ingestion
  - May be disadvantageous for extra-hepatic toxicity, in setting of cerebral edema and in pregnancy (?)
Intravenous versus Oral N-Acetylcysteine

• Retrospective cohort comparing standard IV to PO protocols found no difference in hepatotoxicity
  – 13.9% IV versus 15.8% PO

• Reported lower risk of hepatotoxicity in IV group when started < 12 hours postingestion, greater risk when started ≥ 18 hours postingestion

• 4 deaths (1 IV, 3 PO) occurred in patients where NAC was started ≈20 hours postingestion
Intravenous versus Oral N-Acetylcysteine

- Remaining evaluations comparing IV to PO NAC have failed to demonstrate “advantage” with one regimen

- “...any differences in studies comparing outcomes with IV and oral acetylcysteine were artifactual and likely the result of inappropriate subgroup analysis...”

- Clear benefit associated with starting NAC within 8 hours postingestion

When N-Acetylcysteine Really “Needs” to be Intravenous

- Pregnancy

- Liver failure (acetaminophen-induced)

- Intractable vomiting preventing oral treatment
Duration of Treatment with N-Acetylcysteine

• Initial approach desired methodology to predict duration of therapy based on [APAP]

• Proposed a standard 20-hour duration of treatment with oral NAC
  – Acetaminophen half-life = 4 hours x 5 = 20 hours

• “...FDA reviewers were not comfortable with that length of NAC administration...”

Duration of Treatment with N-Acetylcysteine

- Several durations of treatment for PO NAC have been evaluated: 20, 36, 48, and 72 hours

- Shortened durations of therapy do not increase risk of hepatotoxicity provided liver function tests normal and [APAP] undetectable

- Extended duration of therapy may be required

References:
- Goldfrank’s Toxicologic Emergencies, 9th edition.
Duration of Treatment with N-Acetylcysteineine

• Individualized approach to duration may be most effective

• NAC should be continued until acetaminophen metabolism is complete, [APAP] is undetectable, and no signs of hepatotoxicity
  – Some suggest obtaining [APAP] and hepatotoxicity markers at 24 hours → reassess

### Duration of Treatment with N-Acetylcysteine: Example

<table>
<thead>
<tr>
<th>Time</th>
<th>APAP Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 0</td>
<td>500 mcg/mL</td>
</tr>
<tr>
<td>T+24 hours</td>
<td>7.8 mcg/mL</td>
</tr>
<tr>
<td>T+36 hours</td>
<td>0.97 mcg/mL</td>
</tr>
<tr>
<td>T+40 hours</td>
<td>0.5 mcg/mL</td>
</tr>
</tbody>
</table>
Recommended Intravenous N-Acetylcysteine Regimen

• Intravenous NAC protocol:
  – Loading dose: 150 mg/kg in 200 mL D5W over 60 minutes
  – Maintenance dose #1: 50 mg/kg in 500 mL over 4 hours
  – Maintenance dose #2: 100 mg/kg in 1000 mL over 16 hours

• Volumes must be adjusted for pediatric patients or weight less than 40 kg

• Maximum dose based on 100 kg

Goldfrank’s Toxicologic Emergencies, 9th edition.
Recommended Oral N-Acetylcysteine Regimen

• Oral NAC protocol:
  – Loading dose: 140 mg/kg orally or by enteral tube
  – Maintenance dose: 70 mg/kg every 4 hours x 17 doses; start 4 hours after loading dose

• Dilute to 5% solution

• If vomits within 1 hour, repeat dose
  – Ondansetron can be given as needed

Goldfrank’s Toxicologic Emergencies, 9th edition.
Intravenous versus Oral N-Acetylcysteine: Safety

• Clear difference in safety profile between routes

• Oral route associated with gastrointestinal adverse effects
  – Nausea, vomiting, dysgeusia
  – Patient tolerability → rotten egg smell

• Intravenous route associated with anaphylaxis
  – Rash, pruritus, hypotension, bronchospasm
  – Treat with antihistamines and supportive care

Goldfrank’s Toxicologic Emergencies, 9th edition.
Acetaminophen Toxicity: Special Circumstances

(...because it’s really never that straightforward...)
But Really...We Don’t Know When It Was Taken

<table>
<thead>
<tr>
<th>[APAP]</th>
<th>AST</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>↔</td>
<td>↑</td>
<td>Treat with NAC</td>
</tr>
<tr>
<td>↑</td>
<td>↔</td>
<td>Treat with NAC</td>
</tr>
<tr>
<td>Undetectable</td>
<td>WNL</td>
<td>Do not treat</td>
</tr>
</tbody>
</table>

[APAP]: acetaminophen concentration  
WNL: within normal limits  
↔: regardless of concentration  
AST: aspartate aminotransferase  
NAC: N-acetylcysteine
“Chronic” Acetaminophen Poisoning

• “Chronic” supratherapeutic ingestions may lead to toxicity
  – Generally safer than expected
  – Daily, repeated ingestions of 6—8 grams do not appear to substantially increase risk of hepatotoxicity
  – Series of case reports with daily ingestions of ≥ 4 grams

• No well established evidence or guidelines for chronic exposure

• Future considerations – prescription opioid abuse?
“Chronic” Acetaminophen Poisoning

- High risk groups for chronic poisoning:
  - Increased CYP2E1 activity
  - Decreased glutathione supply and/or turnover
  - Infants with febrile illness
  - Chronic alcohol users and/or malnutrition
  - Concomitant CYP-inducing medications

- \([\text{APAP}] > 10 \text{ mcg/mL}\) and/or elevated AST appear to be at risk and may warrant treatment

References:
- Goldfrank’s Toxicologic Emergencies, 9th edition.
Extended-Release Acetaminophen Product Ingestions

• Designed to deliver both immediate dose and delayed dose of 325 mg

• Majority of acetaminophen released within 4 hours (peak)
  – May result in initial lower [APAP] concentration → “nomogram crossing”
  – Not unique to extended release formulation
  – Recommendation: obtain 4-hour [APAP]

Goldfrank’s Toxicologic Emergencies, 9th edition.
Fat as an antidote...  
...say what?!?! 

(Or, is this a reason to 
eat more bacon?)
Lipid Rescue Therapy: Patient Case 0

• EMS responds to the home of a 17 year-old female found “unresponsive”

• Initial evaluation at the scene reveals:
  - Glasgow Coma Score: 3
  - SpO₂: 91% room air
  - Blood pressure: 108/72 mmHg
  - Blood glucose: 91
  - Respiratory rate: 8 breaths/min
  - Heart rate: 112 bpm

• 5 hours prior to their arrival at the scene, the patient sent a text to a friend saying she was dying

Lipid Rescue Therapy: Patient Case 0

• **Past Medical History**
  – Attention Deficit Disorder
  – Bipolar Disorder

• **Medication History**
  – Amphetamine salts
  – Bupropion
  – Lamotrigine
Lipid Rescue Therapy: Patient Case 0

When the prescription bottles were checked, there was up to **Bupropion XL 7.95 grams** and **Lamotrigine 4 grams** missing.
Lipid Rescue Therapy: Patient Case 0

• A nonrebreather mask was applied and naloxone 2 mg given en route

• The emergency department stay (3 hours) was uneventful
  – Glasgow coma score increased to 6
  – Supportive care provided
  – Initial EKG: QRS 122 msec, QTc 485 msec
  – Patient transferred to intensive care
Lipid Rescue Therapy:
Patient Case 0

• Soon after arrival to ICU, the patient had a tonic-clonic seizure...

• ...followed closely thereafter by pulseless wide complex rhythm...

ACLS measures started –
10 hours post-ingestion
Lipid Rescue Therapy: Patient Case 0

Time 0
ACLS started

T+18 Mins
EKG: pulseless ventricular tachycardia and fibrillation
Interventions: Intubation, Defibrillation x 11, Epinephrine 1 mg x 6, Amiodarone 300 mg, Magnesium 1 gram

T+20 Mins
Interventions: Sodium bicarbonate 50 mEq
Return of spontaneous circulation
Blood Pressure: 84/55 mmHg, Heart Rate: 97 bpm
Lipid Rescue Therapy: Patient Case 0

T + 37 mins

EKG: Pulseless Electrical Activity, Wide Complex
ACLS Resumed

Interventions: Epinephrine 1 mg x 12, Calcium Chloride 1 gram, Sodium Bicarbonate 50 mEq x 2, “High Dose” Norepinephrine and Epinephrine Infusions

Transient pulse detected by Doppler but not sustained

Lipid Rescue Therapy: Patient Case 0

T + 72 mins
- Interventions: 100 mL Bolus of 20% Lipid Emulsion

T + 73 mins
- Return of Spontaneous Circulation

T + 87 mins
- EKG: Normal Sinus Rhythm
- Interventions: Vasopressor Doses Reduced, Sodium Bicarbonate 100 mEq

Lipid Rescue Therapy: Patient Case 0

T + 177 mins

EKG: Pulseless Ventricular Tachycardia
Interventions: Epinephrine 1 mg, CPR x 1 minute

Return of Spontaneous Circulation

T + 24 days

Outcome: Conversant and Talkative, Slight Tremor, Mild Memory Deficits, Fine Motor Incoordination

Disposition: Rehabilitation Therapy
## Lipid Rescue: Patient Case 0

<table>
<thead>
<tr>
<th>Time, Hours</th>
<th>Triglyceride, mg/dL</th>
<th>Bupropion, ng/mL</th>
<th>Lamotrigine, mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5</td>
<td>103</td>
<td>180</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td>11.5</td>
<td></td>
<td>Lipid Bolus</td>
<td></td>
</tr>
<tr>
<td>12.75</td>
<td>681</td>
<td>880</td>
<td>24</td>
</tr>
<tr>
<td>18.25</td>
<td>81</td>
<td>390</td>
<td>21</td>
</tr>
<tr>
<td>28.75</td>
<td>33</td>
<td>62</td>
<td>18</td>
</tr>
</tbody>
</table>
Lipid Rescue Therapy: Patient Case 0

• Fatalities reported after bupropion extended release ingestions of 5.4—9 grams

• Fatal bupropion concentrations reported at 430 and 446 ng/mL

• In large overdose, bupropion exhibits neurologic and cardiac toxicity
Intravenous Lipid Emulsion: Lipid Rescue Therapy

- Proposed lipids would increase susceptibility to local anesthetic systemic toxicity (LAST)
- In rats, found that lipids increased resistance to cardiac arrhythmias from bupivacaine
- Initial reports of success in treating LAST in the operating room

Lipid Rescue Therapy: Case in Point

• Research of non-LAST toxicity in animal models quickly followed
  – Tricylic antidepressants
  – β-blockers
  – Calcium channel blockers

• Numerous animal studies and single patient case reports soon followed
Lipid Rescue Therapy: Case in Point

<table>
<thead>
<tr>
<th>Amitriptyline</th>
<th>Lidocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Organophosphates</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Propanolol</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Ropivacaine</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>

# Lipid Rescue Therapy: Case in Point

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lipid/Aqueous Partition Coefficient (log P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>3.64</td>
</tr>
<tr>
<td>Bupropion</td>
<td>3.47</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>4.71</td>
</tr>
<tr>
<td>Propanolol</td>
<td>3.65</td>
</tr>
</tbody>
</table>

Intravenous Lipid Emulsion: Lipid Rescue Therapy

• Intravascular effects
  – “Lipid sink” theory: increases lipid phase in plasma
  – Lipids bind and extract drug from tissues and plasma

• Intracellular effects
  – Impacts mitochondrial metabolism
  – Saturates fatty acid delivery to increase energy production

• Membrane effects
  – Activates cardiac calcium and potassium channels (?)
  – Increases cardiac myocyte calcium levels

Lipid Rescue Therapy: 
Adverse Clinical Effects

• When used as parental nutrition, reported hypersensitivity, thrombocytopenia, hypercoagulability, pancreatitis, elevated liver enzymes, etc...

• Concern expressed for acute lung injury

• No reported adverse effects outside of temporary lipemia (e.g., blood draws)
Intravenous Lipid Emulsion: “Lipid Rescue Therapy”

“The choice of whether, and when, to initiate LRT is one that is solely discretionary and is based on the clinical judgment of the treating physician. Given the uncertainty of its beneficial effect in human poisonings, it is the opinion of the American College of Medical Toxicology (ACMT) that there are no standard of care requirements to use, or to choose not to use, LRT.”

Intravenous Lipid Emulsion: Lipid Rescue Therapy

• Long-chain triglyceride formulas appear to be most effective (in vitro)

• Recommend 20% lipid emulsion (e.g., Intralipid®)

• Lipid rescue/resuscitation therapy (LRT)
  – Bolus: 1.5 mL/kg intravenously over 2—3 minutes (maximum 100 mL)
  – Continuous infusion: 0.25 mg/kg/min for 30—60 minutes; can increase to 0.5 mg/kg/min

Intravenous Lipid Emulsion: Lipid Rescue Therapy

• Generally considered in life-threatening/ACLS scenarios ➔ “all or nothing”

• Note to self: propofol is not lipid rescue

• Sample kits instructions and to submit cases: http://www.lipidrescue.org
Intravenous Lipid Emulsion: Lipid Rescue Therapy

• Generally considered in life-threatening/ACLS scenarios → "all or nothing"

• Note to self: propofol is not lipid rescue

Sample kits instructions and to submit cases: [http://www.lipidrescue.org](http://www.lipidrescue.org)

Lipid Rescue Therapy: Limitations

- Based on case reports...and rats and dogs
  - Pigs are allergic to lipid emulsion
  - Dose is likely “excessive”

- Overdoses are frequently polypharmacy

- Role – and timing – in therapy?

- Complications and adverse effects?
Updates in Drugs of Abuse

(Or, welcome to chemistry in the 21st century! Just add salt, spice, and herbs to taste.)
Drugs of Abuse:
Welcome to the 21st Century

- Methamphetamine
- Opioids (particularly prescription)
- Other prescription drugs (carisprolol, stimulants, benzodiazepines)
- Synthetic cannabinoids (e.g., spice)
- Synthetic cathinones (e.g., bath salts)
- *Salvia*
- Kratom
- Krokodil
- Piperazines
- And the list goes on and on and on....
But it’s just a plant!

(...and so is foxglove, deadly nightshade, and crab’s eye.)
**Salvia divinorum: Salvinorin A**

- Plant product in mint family, native to Mexico

- Currently not scheduled as controlled substance
  - Several states have enacted legislation to control
  - Currently considered “drug of concern” by DEA

- Widely available on the Internet and “head shops”

- Plant product is chewed or smoked

Drug Enforcement Agency, October 2013
**Salvia divinorum: Salvinorin A**

- Salvinorin A identified as active ingredient
- Potent, selective kappa opioid receptor agonist
- Produces hallucinogenic effects and dysphoria
- Widespread abuse reported in the U.S.
  - Predominantly among young users

Drug Enforcement Agency, October 2013
Salvinorin A: Clinical Effects

• Rapid onset, short duration of effect
  – Inhaled, onset: 30 seconds
  – Chewed, onset: 5—10 minutes
  – Duration: 30—60 minutes

• “Desirable” effects
  – Perceptions of bright lights, vivid colors and shapes
  – Synesthesia
  – Uncontrolled laughter
  – Hallucinations

Drug Enforcement Agency, October 2013
Salvinorin A: Clinical Effects

• Adverse clinical effects
  – Incoordination
  – Dizziness
  – Slurred speech
  – Dysphoria
  – Sedation

• Does not appear to cause respiratory depression
Salvinorin A: Clinical Effects

- Effects appear psychological; no consistent physical findings noted
- Persistent psychosis and depression reported after use
- Questionable addiction/dependence potential
Kratom: Mitragynine

- Derived from *Mitragyna speciosa* tree
- Currently not scheduled as controlled substance
- Widely available on the Internet
- Sold as powder, leaves, and gum that is chewed or smoked or brewed as tea
Kratom: Mitragynine

• Mitragynine produces both opioid and stimulant effects
  – Stimulates post-synaptic alpha-2 and blocks 5HT$_{2A}$ receptors
  – Acts at mu- and delta-opioid receptors
  – Structurally unrelated to known opioids
  – $\approx$13 times more potent than morphine

• Abused for both stimulant and opioid effects and to treat/prevent opioid withdrawal
Kratom: Clinical Effects

- Exhibits dose-dependent effects
  - Low dose: stimulant
  - High dose: opioid effect predominates

- Clinical effects seen in 5—10 minutes, last 2—5 hours

- Withdrawal symptoms and addiction reported in frequent users

Kratom: Clinical Effects

• Acute intoxication mimics opioid ingestion/overdose

• Adverse effects reported by most users
  – Nausea
  – Itching
  – Sweating
  – Dry mouth
  – Constipation
  – Anorexia

Kratom: Clinical Effects

• Seizures, coma, and deaths have been reported

• Particular concern is “Krypton”
  – Kratom mixed with O-desmethyltramadol
  – Sold in large quantities (e.g., 50 gram containers)
  – Autopsy findings of pulmonary edema

• Naloxone can be considered for reversal

See You Later, Aligator...
...After a While Krokodil!
Krokodil

• “Homemade” heroin

• Reports emerged in Russia where use is widespread
  – Heroin very expensive and/or unavailable
  – Codeine over-the-counter

• Named “krokodil” because of skin appearance after use
Krokodil

• Initially produced in the US in 1930
  – Already considered schedule I substance by the DEA

• Easily produced by combining codeine with gasoline, paint thinner, iodine, hydrochloric acid and red phosphorous
Krokodil

- Generally abused as heroin substitute
- Reported use as opioid substitute when drug of choice not available
- High degree of addiction liability
- Two samples tested positive in 2004 in the U.S., no “confirmed” reports since that time
Conclusions

• Intravenous and oral N-acetylcysteine are equally efficacious for acetaminophen poisoning...particularly when started “early”

• Intravenous lipid emulsion – “lipid rescue” – shows promise in refractory poisonings

• New drugs of abuse are concerning for significant toxicity, particularly among young users
Compared to the PO route of administration, which of the following statements regarding the IV route of administration of NAC for the treatment of APAP toxicity is true?

A. IV NAC has superior efficacy for acute APAP toxicity

B. IV NAC has fewer adverse effects

C. IV NAC is preferred in APAP-induced acute liver failure

D. IV NAC is contraindicated in pregnancy
Intravenous lipid emulsion (20%) may be an effective antidote for toxicity associated with which of the following?

A. Propanolol
B. Oxycodone
C. Acetaminophen
D. All of the above
Which of the following clinical presentations is most consistent with ingestion of Kratom (mitragynine)?

A. Nausea, vomiting, and hepatotoxicity

B. Hallucinations, agitation, and tachycardia

C. Sedation, diaphoresis, and seizure

D. Miosis, respiratory depression, and tissue necrosis
Questions?!?!
Selected References – N-Acetylcysteine


Selected References –
N-Acetylcysteine


Selected References – N-Acetylcysteine


Selected References – N-Acetylcysteine


• Kociancic T, Reed MD. Acetaminophen intoxication and length of treatment: how long is long enough? *Pharmacotherapy* 2003; 23: 1052-1059.
Selected References – N-Acetylcysteine


Selected References – Lipid Rescue Therapy


Selected References – Lipid Rescue Therapy


Selected References – Lipid Rescue Therapy


Selected References – *Salvia divinorum*

Selected References – *Salvia divinorum*

Selected References – Kratom


Selected References – Kratom


Selected References – Krokodil (Desomorphine)
