Alternative Dosing Strategies for N-acetylcysteine in Acetaminophen Overdose

aka -Individualizing NAC treatment for your site or your patient

Learning assessment Question #1

- Which one of the following statements about the basis of n-acetylcysteine (NAC) dosing for APAP poisonings is true?
  A. US and UK dosing strategies are based on human dosing ranging pharmacokinetic studies
  B. Dosing is based on replacing glutathione stores based on observations of human hepatic glutathione depletion in APAP OD'ed patients
  C. It became a violation of state law to use inhalational NAC product and administer it intravenously after the FDA approved product was released
  D. The FDA approved regimen for iv-NAC (Acetadote) specifies a three bag regimen

Learning Assessment Question #2

- Which one of the following represents a factor not yet considered or resolved in considering the use of NAC for APAP OD?
  A. The effect on infusion rate on anaphylactoid reactions with IV NAC
  B. What should be the treatment endpoint?
  C. What is better to use, patient weight or dose ingested to base dosing upon
  D. All are true

Learning assessment Question #3

- Which one of the following items represents a setting where unconventional dosing regimens can be considered?
  A. Inadequate supply of IV NAC to prepare for one day's therapy
  B. Patient is being transferred to a transplant center
  C. Patient is a child
  D. All are true

Objectives

1. Explain the rationale for the original intravenous NAC dosing regimen in the UK, the original oral regimen using the FDA approved inhalational product in the US and current practices utilizing varying routes, numbers of intravenous bags or doses or dosing rates.
2. Outline risk factors not yet considered in these regimens that may explain and or be used to modify the regimen in an individualized patient at initiation or during therapy
3. Justify an individualized regimen choice from current practices on the basis of location, supply, patient prognosis, risk factors and patient response

Disclosure

- I have no conflicts of interest with any of the products or devices mentioned or discussed in this presentation

- I do confess to a great interest in conflict and hope to stir some discussion though

Background and context

- Failed engineer, occupational sociology trained, BS Pharm, Drug Info pharmacist, PharmD, residency, PK/id fellowship, IM nephrology pharmacist, EM RPh, EM/Tox RPh, PGY2/Fellowship PD, PGY1 RPD/Tox RPH
- Attending in Toxikon Consortium faculty
- If I say something is “voodoo” medicine it means it is made up but sounds logical enough that people believe it and events support it being correct more often than not. Sometimes referred to as “eminence-based medicine”

APAP OD and dosing NAC: This used to be easy

- 140mg/kg oral once then 70mg /kg q 4hr for 17 doses
  - Started after 4 hr Cp confirmed “above the line”
    - *The original proposed line started at a 4hr Cp of 200mg/l*
    - *FDA adapted by adding 2nd lower line starting 150mg/l*
    - *In UK another lower line added starting at 100mg/l*
  - Diluted in non-alcoholic beverage, in a lidded container and a taped in place straw to increase palatability and decrease odor
    - Fresca commonly written, fruit punch drinks are my voodoo choice
    - *Anyone ever heard of olfactory paralysis or fatigue? Why do we think it only happened with H_2S gas? And isn’t H_2S what makes NAC smell?*
  - Any doses vomited within one hour of administration orally were repeated. If vomiting occurred again then switch to IV or pretreat with anti-emetics

What is done conventionally

Regimen

- Original PO: 140mg/kg once then 70mg/kg q 4 x 17 doses
- Original IV (UK): 150mg/kg over 15min (600mg/kg/hr) then 12.5mg/kg/hr x 4hr, then 6.25mg/kg/hr
- IV n-acetylcysteine (Acetadote US): 150mg/kg over 1 hour, then 12.5 and 6.25 as per UK+, three separate bags *(or two or one or for 24 hours)*

Rate and 20 hr Total

- Maintenance = 17.5 mg/kg/hr
  - Total with 5 maintenance= 490mg/kg (420 with 4 doses)
- Maintenance = 6.25 mg/kg/hr
  - Total = 300mg/kg
- Same as UK IV

NAC IV in the US prior to 2004

- Dose drawn from 20% vial drawn then injected through a 0.22u filter needle into 100ml bag and diluted to 100ml with NS
  - Could inject into bag and then place 0.22u filter between bag and pump but back pressure failures in pumps at that time made this less practical.
  - Individual bags for every dose
- Therapy very commonly delayed while awaiting initial acetaminophen concentration (estimated availability time for laboratory to finish testing) within a cutoff of 8 hours post time of ingestion)
  - At UIC pharmacy had its own assay machine and had results in 30-45 minutes after drawing blood. So we would start empiric NAC only if presentation was 6-7 hours after ingestion time
- Switch back to PO as soon as patient could tolerate it

APAP OD and dosing NAC: This used to be easy but

- 140mg/kg PO or IV once then 70mg /kg q 4hr for 17 doses
  - Started after 4 hr Cp confirmed “above the line” (if anticipated time of result was under 8hrs post exposure)
  - Any doses vomited within one hour of administration orally were repeated. If vomiting occurred again then switch to IV or pretreat with anti-emetic and try again
- If a serious co-ingestant existed, doses were staggered very 2hr with activated charcoal
  - NAC doses increased by 40% based on volunteer data
  - Mostly driven by need in APAP OD combined with ASA or theophylline overdoses
- If hemodialysis was indicated NAC doses were doubled (maintenance IV NAC dose thus 35mg/kg/hr)

APAP OD and dosing NAC: This used to be easy but

- 140mg/kg PO or IV once, then 70mg /kg q 4hr for 17 doses
- If a serious co-ingestant existed, doses were staggered with activated charcoal, NAC doses increased by 40% (largest reported decrease AUC of NAC when given following AC in volunteer studies – Ekins etall. AJEM 1987;5:483-7)
- With concomitant HD, NAC doses are doubled
- Patients presented > 24 hours post ingestion – treat anyway

APAP OD and dosing NAC: This used to be easy but

- 140mg/kg PO or IV once, then 70mg /kg q 4hr for 17 doses
- If a serious co-ingestant existed, doses were staggered with activated charcoal, NAC doses increased by 40%
- With concomitant HD, NAC doses were doubled
- Patients presented > 24 hours post ingestion – treat anyway
- Therapy duration lengths were empirically reduced from 72 to 48 to 36 to 24 to 20 hours
  - Usually one inadequately sized study concludes “equivalent” benefit and then adopted by almost everyone almost as if we had Twitter available
  - More formalized as “Patient tailored treatment” Dart, Rumack Ann Emerg Med 2007;50:280-281

Summary of dosing up to 2004

Regimen

- PO (US): 140/mg/kg load, then 70/mg/kg x 17 doses
  - If with AC (inc 40%)
  - If HD (inc 100%)
  - Shorter courses
- IV: 150mg/kg/hr x 1hr, then 12.5mg/kg/hr x 4hr then 6.25mg/kg/hr x 16hr
  - Doubled for HD

Fastest rate and total dose

- 140/4 = 35 mg/kg/hr PO and total 1330mg/kg
  - 204/4 = 51mg/kg/hr PO
  - 280/4 =70mg/kg
  - Varied by length but no less than 420mg/kg
- Fastest rate would be
  - 300mg/kg/hr for load
  - 25mg/kg/hr for "2nd bag"

What was done situationally 1978-2004

Regimen

- US pre-IV: 140mg/kg over 1h then 70mg/kg over 1 hr q 4 x 17 doses

- Original IV (UK): 150mg/kg over 1 hour then 12.5mg/kg/hr x 4hr 6.25mg/kg/hr

Rate and 20 hr Total

- Max rate 280mg/kg/hr, total 1330mg/kg over 72 hours

2004: IV N-acetylcysteine (Acetadote) approved by FDA

- Heavily promoted with an emphasis on
  - Only FDA approved intravenous product for APAP OD in a three bag sequence
  - By FDA regulation 797, inhalational NAC given IV is a “compounded” product and thus not considered FDA approved.
  - But this is considered a State regulatory issue and definitions vary by state.
  - There is no FDA language that requires the use of IV-NAC in the absence of a contraindication to the oral route
- Has essentially eliminated all inhalational product use IV or PO for APAP OD

The stage is set

Individualizing therapy with NAC

- The basic goal of NAC therapy is NOT a rigid dosing strategy
  - It should improve outcomes
  - Patient responses should determine changes to dosing schemes
  - Unfortunately, the trend is to
    - Only use intravenous route
    - Argue over preferred number of bags (b/c of order sets?)
    - Default to weight-based dosing (*hmmm weigh more = less toxin/kg means give more antidote? Isn't this the problem with charcoal dosing again?)*
    - *Are we prefering anaphylactoid reactions to nausea (bit overstated)*
  - And what endpoint/s do we use as outcomes measures?
  - NAC's role/ relationship with fomepizole (4-MP)
  - Can NAC be bad in APAP OD?

Origin of dosing schedules

- Animal studies in the 1970's suggested that a sulfhydryl nucleophile would be beneficial, proven true with cysteamine
- 70% glutathione liver content depletion was associated with hepatic necrosis= 4.2 mmol/L
- Human livers average 1.5 L so NAC dose was determined to need to replace sulfhydryl content 6mmol of glutathione = 6mg/kg of NAC. FDA wanted a safety factor and increased to 140mg/kg load and 70mg/kg q 4 or 17.5 mg/kg/hr
  - *Healthy animals, well nourished, no other drugs, normal livers)*

Origin of treatment duration

- UK therapy duration chosen as 20.25 hrs to approximate a 4 hour half-life of acetaminophen
  - Observations that some patients “relapsed” with increases in ALT and AST lead to duration extensions (outcome measures and durations never stated nor studied)
  - Late 80s two case series showed that late administration of NAC in delayed presentations with **fulminant hepatic** failure was associated with decreased mortality, cerebral edema and AKI.
    - This is now used as basis for the 100mg/l lowest third line on nomogram used in England
- US duration – duration felt too short, longer half lives had been seen. Used 12 hrs (based on increased mortality observations) proposed 60hrs to FDA which extended to 72hrs to be conservative

Adverse effects

- Heard K. Clin Tox 2010; 2009;48:424-430
  - Toxic Investigator Network registry data – II US hospitals
  - Retrospective chart review 503 patients: 306 iv, 145 po and 52 both
  - Overall results:
    - IV route had fewer ADE versus PO (26. 3% vs 37.5%, 95% CI 3.3-19.2)
    - There were no serious NAC-related ADEs in either group only 35% were NAC-related
    - Of 169 patients with ≥ 1 ADE, 19 IV and 25 PO were switched to the alternative route
      - Only 12 due to a NAC-related ADE (but they didn't specify which route these came from)
      - Assuming all were the PO route - 12/173 patients getting PO or switched from PO (7%)
    - Overall, IV had less GI ADE vs PO (adj for NAC related 13.5% vs 26.9%)
    - PO had less anaphylactoid than IV (adj for NAC-related 0% vs 5.8%)
- *So should the ADE as outcome really be an outcome?*

Outcomes to monitor

- Death
  - #case/yr/hosp
- ALT AST
  - Absolute: < 1000? 500? 3x ULN?, “normal”, < 100?
  - Urinary protein adducts – still primarily a research tool
  - Half-life
    - Alt and AST have separate and disparate half-lives (47hrs and 17hrs respectively)
      - *Really willing to wait 3-5 half-lives for normal ALT? (141 – 235 hrs)*
    - Are they improving b/c there is so little tissue mass left?
    - Ethanol? Why isn’t ethanol concentrations reported or studied?

Bags – How many?

- No number is ideal nor universal
- Questions whose answers determine the choice:
  - First and most important (to me)…Can they take oral route?
    - NG or feeding tube in place?
  - Patient location
    - Needs transfer
    - Primary treatment site for low acuity care
  - Supplies
    - Drug shortages
  - Time of ingestion and anticipated time of first APAP concentration result
  - I don’t think any one number of bags is safer and I don’t worry about cost
  - *Have we had a recent med error?*

NAC and 4-MP? NAC maybe bad?

- Akakpo et al. Arch Toxicol 2022 doi: 10.1007/s00204-021-03211-z
- This recent reviews provides background for
  - MOA
    - NAC and 4MP minimize acute injury but 4-MP also assists with hepatic regeneration
      - Murine models support that late and excess NAC down regulates hepatic biogenesis
      - Anecdotally supported by early “late” treatment study where survival and cerebral edema improved but there was no change in hepatic recovery
    - But seems to require that and excess of NAC is being delivered and threshold is unknown

Summary

- Well NAC dosing is a mess
- Treatment of APAP is also and getting worse
  - We need clinically practical and meaningful monitoring parameters
  - Growing trend to use “markers” that can easily allow statistical power in small studies that are unrelated to overall major outcomes should stop or at least their findings should not be primary determinants for treatment plans
- Dosing strategies should be thoughtful and not standardized
- But we don’t know how to do that currently

Nice try Frank but we need to know what to do

- Well, I like…
  - To use PO route whenever possible
  - If I have supply issues for a dose, why not both routes concomitantly
  - To use the 8 hour window to take advantage of getting a real Cp to assess
    - I worry about Cps $\geq$ 400 at 4hrs (with a t1/2 $\geq$ 4 hrs)
    - And I give more drug here and willing to go to at least 25/g/kg/hr (comfy to 35)
    - If ALT and AST rise after NAC started, I look for excuses to increase the dose
  - I ask and worry about nutrition
  - I like to monitor CP and ALT/AST (since easily available)
    - I start thinking stop NAC when APAP <30mg/l and ALT and AST are both declining over at least three determinations

Learning assessment Question #1

- Which one of the following statements about the basis of n-acetylcysteine (NAC) dosing for APAP poisonings is true?
  A. US and UK dosing strategies are based on human dosing ranging pharmacokinetic studies
  B. Dosing is based on replacing glutathione stores based on observations of human hepatic glutathione depletion in APAP OD'ed patients
  C. It became a violation of state law to use inhalational NAC product and administer it intravenously after the FDA approved product was released
  D. The FDA approved regimen for iv-NAC (Acetadote) specifies a three bag regimen

Learning Assessment Question #2

- Which one of the following represents a factor not yet considered or resolved in considering the use of NAC for APAP OD?
  A. The effect on infusion rate on anaphylactoid reactions with IV NAC
  B. What should be the treatment endpoint?
  C. What is better to use, patient weight or dose ingested to base dosing upon
  D. All are true

Learning assessment Question #3

- Which one of the following items represents a setting where unconventional dosing regimens can be considered?
  A. Inadequate supply of IV NAC to prepare for one day's therapy
  B. Patient is being transferred to a transplant center
  C. Patient is a child
  D. All are true