Poison/Potion/Placebo?
N-Acetyl Cysteine
Getting the kNACk of non-paracetamol induced acute liver failure

Nepean WTET summary 14/7/20

Background and Rationale

- N acetyl cysteine (NAC) replenishes mitochondrial and cytosolic glutathione stores preventing accumulation of toxic metabolites (NAPQI in acetaminophen/paracetamol toxicity by facilitating non-toxic sulfate conjugation). It is the specific antidote for paracetamol toxicity and thereby forms first line treatment for a patient presenting with paracetamol-induced acute liver failure (ALF)
- Supportive management forms the mainstay of treatment for most non-paracetamol ALF not requiring emergent transplantation. However NAC has a number of properties beyond preventing accumulation of toxic metabolites that may be useful in ALF of other causes; mechanisms e.g. anti-inflammatory, anti-oxidant properties alongside inodilatory properties (improve microcirculatory blood flow and O2 delivery) and improved lung compliance. Animal RCTs show increase in cerebral perfusion pressure

Advantages and Disadvantages

- Advantages
    - Potential benefits; anti-oxidant, anti-inflammatory and improved oxygen delivery (inodilatory) to tissues
    - Cerebral oedema main mode of death in ALF; increased CPP may be helpful if true
- Disadvantages
    - Administration usually requires a large volume load (risk worsening oedema)
    - ALF usually presents with hyperdynamic state; is inodilation really useful here?
    - Made-up in 5% dextrose; – risk harm by hyponatraemia worsening cerebral oedema
    - Severe anaphylactoid reactions occur (can cause severe hypotension, -not harmless)

Key studies

- **Harrison 1991 NEJM**
    - NAC increased cardiac index and thereby MAP -despite decreasing SVR. It increased O2 delivery, consumption and extraction
- ***Kortsalioudaki; Liver Transplantation; 2008*** *(paediatric study; King's London)*
    - *Retrospective review of safety and efficacy; standard care (1989-1994, n=59) and standard care + NAC (1995-2004; n=111). NAC group received 100mg/kg/24h continuous infusion until INR<1.4, death or transplantation*
    - *Shorter LOS (25d vs 19d, P=0.05), higher survival with native liver (22% vs 43%, P=0.005) and fewer died after liver transplant (39% vs 6%, P=0.02; NB improved with time) with NAC*
    - *NB more exchange transfusion and intracranial bolts in control and more inotropic support and haemofiltration in NAC groups may represent changes in 'standard care' over time*
- **Mumtaz; Hepatol Int; 2009** (Pakistan)

- Single center prospective (2004-2007, n=47) study, with retrospective controls (2000-2003, n=44). Excluded paracetamol use (incl. in some viral ALF), acute on chronic liver disease, or refused consent (prospective). Standard treatment +/- NAC (received oral NAC 140mg/kg followed by 70mg/kg; 17 doses, 4h apart, started within 6h of admission)
- Primary outcome survival without liver transplantation; 47% in NAC group, vs 27% (P=0.05)
- Hepatitis E&B main causes of ALF; NAC group younger (27.74y vs 37.52y) but higher bili and more high-grade encephalopathy with more needing ICU & mech. Ventilation

- **Lee; Gastroenterology; 2009** (Texas)
  - MC RCT DB. NAC (in 5% dextrose) vs placebo (5% dextrose) for 72h. NAC dose 150mg/kg/h over 1h, 12.5mg/kg/h for 4h then continuous 6.25mg/kg for remaining 67h. Stratified by encephalopathy grade (1-2 vs 3-4) and site. Excl. from NAC arm if ischaemic, pregnancy or malignant aetiology. N=173 (92 placebo vs 81 NAC) from 22 sites
  - Primary outcome; survival at 3w; 70% vs 66% (P=0.283). But significant transplant-free survival 40% vs 27% (P=0.043); specifically though this was weighted by early encephalopathy (low grade; 1-2) group
  - Similar groups, transplant rates high! 32% in NAC vs 45% placebo
- ***Squires; Hepatology; 2013*** *(paediatric study; North America and USA)*
  - *MC RCT DB; adaptive allocation within strata by age (<2 vs 2-17) and encephalopathy grade (1-2 vs 3-4). Randomised to NAC (150mg/kg/d in 5% dextrose vs 5% dextrose for up to 7d. Paediatric liver transplant centers only (20); n=184 (over 9y)*
  - *Primary outcome; survival at 1y 73% (NAC) vs 82% (placebo), P=0.19 (with no difference in lower hepatic encephalopathy grade). Note 1y transplant-free survival was significantly less in children who received NAC (35% vs 53%, P=0.03)*
  - *Aetiology different from adults (54% indeterminate), pathophys may differ (metabolic, xenobiotic), different immune responses between adult and children?*
- **Nabi; Saudi J Gastro; 2017** (India)
  - RCT adults with fulminant hepatic failure (rather than just ALF; so encephalopathy <8weeks) NAC (150mg/kg over 1h, 12.5mg/kg/h for 4h followed by 6.25mg/kg/h for remaining 67h) vs 5% dextrose alone; for total of 72h; excl. ischaemic, pregnancy and acute-on-chronic aetiologies. Non-transplant center; n=80 (40/40)
  - Increased survival (72.5% vs 47.5%, P=0.025) & shorter hospital stay in survivors with NAC
  - Mainly indeterminate aetiology (32.5% & 42.5%) and then hepatitis E. NAC group had worse baseline. But ?they didn't specify what their primary endpoint was in advance?…

Summary (my practice)

- High quality prospective RCTs in adults are lacking. The external validity of those performed are possibly not translatable to my usual population (hepatitis E uncommon in Australasian ICUs; exclusion of ischaemic or decompensation of chronic disease which form a high proportion)
- Above studies documented minimal adverse events however with giving NAC; it is safe!
- My usual practice therefore (until better studies become available) is to give NAC unless contraindicated (or specific risk/concerns) with the following provisos;
  - I make it up in 0.9% NaCl to defend the sodium as part of neuroprotection (mitigating risk of cerebral oedema); whilst most guidelines say it should be reconstituted in 5% dextrose, my experience from transplant centers is it is safe to make-up and give in 0.9% NaCl
  - I give 100mg/kg/d (lower dose; reduced risk of hypotension/anaphylactoid reaction) for up to 72h only, and I give this in lieu of maintenance fluid to minimise the risk of volume overload. I review the benefit-harm of continuing (with regards to volume) once feeds are established if this occurs <72h and stop it if input volumes are a concern
  - I start early (low probability of benefit if late) but stop at any time if harm outweighs benefit
  - I do not have experience of giving enteral NAC to this group