Clinical Pharmacology & Toxicology Pearl of the Week

~ Newer IV NAC regimens, Part 1 ~

Case:

- ✓ A 25-year-old female ingested a supratherapeutic amount of acetaminophen (APAP) at 10am.
- ✓ The 4-hour APAP concentration was 1200 umol/L, indicating that hepatotoxicity (serum AST or ALT > 1000) was likely.
- ✓ The patient was started on IV N-acetylcysteine (NAC) and made a full recovery. No evidence of hepatotoxicity was seen during her hospital stay.

Background:

- ✓ The traditional IV NAC regimen is a 3-bag protocol consisting of a 150 mg/kg loading dose over at least 60 minutes, 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours.
- ✓ While IV NAC is a safe and effective antidote, there are some challenges with its use. These include the following:
  - GI adverse effects (nausea, vomiting, retching)
  - Anaphylactoid reactions
  - Medication errors, especially with the traditional 3 bag regimen
    - Incorrect dose (preparation/mixing errors)
    - Administration delays
  - Dose adjustment for patients with hepatotoxicity or on dialysis
  - Poison centre recommendations to double/triple NAC dose not followed by bedside
- ✓ Newer IV NAC regimens have been developed to try and address these issues by lowering the dose and rate of the first infusion, administering fewer bags, and rechecking laboratory tests at 12 hours into the infusion to determine if those at low risk can have their NAC stopped.
- ✓ This two-part series of Pearls will describe, compare, and contrast these newer IV NAC regimens

Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol (SNAP) regimen:

- ✓ Loading dose: 100 mg/kg over 2 hours
- ✓ Then 200 mg/kg over the next 10 hours
  - Repeat this dose for bag 3 and beyond as needed (double dose if higher risk)
- ✓ Stopping criteria:
- ✓ Compared to traditional 3 bag regimen:
  - Fewer adverse events (anaphylactoid reactions and GI adverse effects)
  - Non-inferior in preventing acute liver injury

Australia and New Zealand 2-bag regimen:

- ✓ Loading dose: 200 mg/kg over 4 hours
- ✓ Then 100 mg/kg over 16 hours
  - Repeat this dose for bag 3 and beyond if needed (double dose if higher risk)
- ✓ Stopping criteria:
- ✓ Compared to traditional 3 bag regimen:
  - Fewer adverse events (anaphylactoid reactions and GI adverse effects)
  - Non-inferior in preventing acute liver injury

Ontario Poison Centre regimen:

- ✓ Loading dose: 240 mg/kg over 4 hours
- ✓ Then 6 mg/kg/hr for at least 8 hours and when stopping criteria met
    - Use 12 mg/kg/hr if patient is higher risk based on [APAP], liver enzymes, blood gases, and clinical status
- ✓ Stopping criteria:

"Two-step" regimen (used in Alberta, Saskatchewan, and Northwest Territories):

- One concentration (30 mg/ml) in one IV bag
- Loading dose: 150 mg/kg over 1 hour
- Then 15 mg/kg/hr over 20 hours
    - Continue this infusion rate until stopping criteria met
        - INR < 2
        - [APAP] undetectable
        - Aminotransferases normal or declining
        - Patient not encephalopathic
        - Creatinine normal or declining
- Compared to traditional 3 bag regimen:
    - Fewer anaphylactoid reactions
    - Decreased hepatotoxicity in high-risk patients
    - Less need to adjust infusion rate during hemodialysis or hepatotoxicity

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).

References:

1. Ferner R. E. et al. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. Br J Clin Pharmacol. 52:573-577. 2001.
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3. Hernandez SH et al. The Pharmacokinetics and Extracorporeal Removal of NAC during renal replacement therapies. Clin Tox. 53(10): 941-949, 2015.
4. Johnson MT et al. Evaluation of a Simplified N-Acetylcysteine Dosing Regimen for the Treatment of Acetaminophen Toxicity. Annals Pharmacol 45:713-720. 2011.
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7. Chiew et al. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clinical Toxicology 2017. DOI: 10.1080/15563650.2017.1334915