Clinical Pharmacology & Toxicology Pearl of the Week

~ N-acetylcysteine and Anaphylactoid Reactions ~

- ✓ N-acetylcysteine (NAC) is the antidote of choice for treatment of acetaminophen (APAP) toxicity.
- ✓ It has several mechanisms of action when used for APAP toxicity, including: glutathione precursor, glutathione substitute, acting as a substrate for sulfation, and enhancing reduction of NAPQI (toxic metabolite) to acetaminophen.
- ✓ In patients with hepatotoxicity, it increases free radical scavenging, increases ATP production, and improves hepatic oxygen delivery and blood flow.
- ✓ Anaphylactoid reactions to IV NAC are well-described in the literature. The incidence of such reactions is about 8%.
- ✓ The mechanism is believed to involve either non-IgE mediated histamine release or direct complement activation.
- ✓ Unlike true anaphylaxis, prior exposure to NAC is not required, nor is continued or future treatment contraindicated.
- ✓ Symptoms include cutaneous features (urticaria, flushing, pruritus, angioedema), respiratory features (cough, wheeze, dyspnea), and in severe cases, hypotension and cardiac arrest.
- ✓ Several factors are associated with an increased risk of anaphylactoid reactions to NAC, including:
    - history of asthma or atopic disease
    - family history of allergy
    - lower acetaminophen concentrations on admission (APAP decreases histamine release from mononucleocytes and mast cells in a dose-dependent manner)
    - female sex
    - younger age
    - lower alcohol consumption
    - a history of previous reaction to NAC
    - administering the loading dose over any time shorter than 60 minutes
    - longer time interval from ingestion to treatment with NAC

- ✓ Suggestions for managing anaphylactoid reactions to IV NAC include:
    - no specific treatment and no change in the NAC infusion if the only symptom is flushing.
    - diphenhydramine 1 mg/kg intravenously for urticaria.
    - diphenhydramine and holding the infusion for one hour for angioedema.
    - diphenhydramine, holding the infusion, and consideration of epinephrine for respiratory symptoms or hypotension.
    - fluid boluses, corticosteroids and beta-2 agonists can also be considered for patients with respiratory symptoms and hypotension.
    - if no symptoms reappear after one hour after stopping the infusion, the NAC infusion be restarted.
    - pretreatment with an antihistamine may also be considered in patients who have previously developed reactions.

- ✓ If reactions reappear after IV NAC is restarted, switching to oral NAC may be an option. While nausea and vomiting are common with oral NAC, rash and other features of anaphylactoid reactions are extremely uncommon.

- ✓ Newer randomized trials with slower loads of NAC or different dosing schedules have shown fewer adverse effects (especially vomiting or retching, as well as anaphylactoid reactions).

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

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). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

Created: April 12, 2019

Reviewed: Feb 19, 2025