Clinical Pharmacology & Toxicology Pearl of the Week

~ Nitrofurantoin ~

- ✓ Nitrofurantoin (Macrobid) is a nitrofuran antimicrobial that is commonly used to treat uncomplicated urinary tract infections.
- ✓ It has a unique mechanism of action:
  - The parent drug is taken up and reduced by bacterial proteins into reactive intermediates that inactivate or alter bacterial ribosomes, leading to inhibition of protein synthesis, aerobic metabolism, DNA, RNA, and cell wall synthesis.
- ✓ Nitrofurantoin has a broad spectrum of activity, with minimal bacterial resistance due to its multi-modal mechanisms of action.
- ✓ Nitrofurantoin is bactericidal in the urine at therapeutic doses, however, is ineffective at treating any other type of infection as it concentrates in the urine only.
- ✓ It is indicated for use in patients with a creatinine clearance of >60 mL/minute, and therefore should not be used in those with renal impairment.

Nitrofurantoin pharmacokinetics:

- Good oral bioavailability (60-90%), especially when taken with food (food increases absorption by up to 40%)
- Nitrofurantoin has a Vd= 0.8L/kg, which is moderate
- Up to 60% of the drug is metabolized into inactive metabolites by body tissues (no CYP interactions)
- The drug and its metabolites are excreted, and therefore concentrated, in the urine.
- Nitrofurantoin has a half-life of 20-60 minutes depending on formulation

- ✓ Nitrofurantoin has been associated with numerous serious adverse effects, including:
  - Bacterial superinfection (C. Diff colitis, although this is a low risk drug for this)
  - Hemolysis in those with G6PD-deficiency
  - Peripheral neuropathy
  - Acute hepatitis (hepatocellular with a hypersensitivity-type reaction &/or cholestatic jaundice)
  - Pulmonary toxicity -
    - Acute pneumonitis
    - Subacute lung disease
    - Chronic interstitial lung disease (with chronic use)

Serious Adverse Events:

- ✓ **Hemolysis in patients with G6PD-deficiency:**
  - G6PD-deficiency is x-linked, more likely to affect men than women, and is most prevalent among people of Mediterranean and African heritage.
  - G6PD-deficient erythrocytes are uniquely sensitive to any extra oxidative stress as they do not regenerate NADPH appropriately (and subsequently glutathione) like individuals with normal G6PD enzyme activity.
  - Nitrofurantoin causes oxidative stress in the red blood cell, and therefore in those with G6PD-deficiency, can cause intravascular and extravascular hemolysis upon initiation of therapy.
- ✓ **Peripheral neuropathy**
  - Nitrofurantoin is known to cause axonal toxicity leading to a peripheral neuropathy that is often reversible provided the drug is stopped quickly following symptom onset.
  - The risk is increased in those on greater than 5 days of therapy and in elderly patients with reduced renal function (CrCl<60), although the incidence is considered rare (1 in 150,000).
- ✓ **Hepatitis**
  - Acute and chronic forms of nitrofurantoin-induced hepatitis are known to occur, especially in those who have prolonged exposure to the drug.
  - The acute form is more common, and often presents with hepatocellular LFTs and serology that mimics an autoimmune hepatitis (positive ANA, Anti-Smooth Muscle Antibody and elevated IgG are often present); cholestatic injury is less common but is also known to occur following prolonged use of the drug.
- ✓ **Pulmonary toxicity**
  - Acute pneumonitis occurs on average within 7-9 days of initiating the drug (and within 24 hours in those with previous exposure to the drug) and is not dose dependent. It is due to a type-I or Type-III hypersensitivity reaction that is characterized by fever, dyspnea, dry cough, and bibasilar infiltrates on imaging with peripheral neutrophilia, eosinophilia (both peripheral and in alveolar fluid) and a maculopapular rash.
  - Chronic interstitial lung disease is less common and occurs after a few months of therapy. Symptoms include dyspnea, dry cough, and fatigue. Imaging often reveals bilateral reticular ground-glass opacities with diffuse pneumonitis; it can also manifest as Cryptogenic Organizing Pneumonia (COP), Eosinophilic Pneumonia (EP) and Non-Specific Interstitial Pneumonia (NSIP).
- ✓ **Nephritis**
  - Nitrofurantoin is also recognized as causing acute interstitial nephritis (AIN), especially in those with reduced creatinine clearance. This manifests with acute kidney injury, white blood cells (and sometimes red blood cells) in the urine, white cell casts, peripheral &/or urine eosinophilia, fever, and flu-like symptoms.

References:

1. CMAJ June 16, 2015 187 (9) 648-656; DOI: https://doi.org/10.1503/cmaj.150067
2. Sakaan SA, Twilla JD, Usery JB, Winton JC, Self TH. Nitrofurantoin-Induced Hepatotoxicity. Southern Medical Journal. 2014;107(2):107–113. doi: 10.1097/SMJ.0000000000000059.
3. https://www.rxfiles.ca/rxfiles/uploads/documents/Nitrofurantoin-Peripheral-Neuropathy.pdf
4. Pamba, A., Richardson, N. D., Carter, N., Duparc, S., Premji, Z., Tiono, A. B., & Luzzatto, L. (2012). Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase–deficient children receiving dapsone. Blood, 120(20), 4123-4133. Accessed September 09, 2019. https://doi.org/10.1182/blood-2012-03-416032.

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 September 4, 2019
Reviewed February 21, 2025