



# Clinical Pharmacology & Toxicology Pearl of the Week

## Nitrofurantoin – Part 2: Serious Adverse Effects

### ✓ 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.



The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click [HERE](#) for clinical issues the CP service can assist with.



The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

### References:

1. Sakaan SA, Twilla JD, Utery JB, Winton JC, Self TH. Nitrofurantoin-Induced Hepatotoxicity. Southern Medical Journal. 2014;107(2):107-113. doi: 10.1097/SMJ.0000000000000059.
2. <https://www.rxfiles.ca/rxfiles/uploads/documents/Nitrofurantoin-Peripheral-Neuropathy.pdf>
3. 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>.
4. <https://www.pharmacytimes.com/contributor/dewilka-simons/2018/01/guide-to-g6pd-deficiency>

5. <https://www.uptodate.com/contents/nitrofurantoin-induced-pulmonary-injury#H328868544>