Introduction

- Metronidazole is a commonly utilized antibiotic; considered a Top 200 drug based on prescriptions.
- It is typically well-tolerated and used to treat a broad spectrum of infections across all ages.
- Side effects are usually minimal.
- Similar to other antimicrobials (e.g., GI symptoms), and are usually dose-dependent.
- Normally resolve with drug discontinuation.
- Prior case reports demonstrate neuropathy as a potential side effect—mostly seen with higher doses.
- Neuropathy often requires doses between 12 and 228 grams of metronidazole.
- It oftentimes persists long after drug discontinuation.

Case Presentation

- 45 year old female without relevant PMHx presented with burning and excruciating pain in a stocking-and-glove distribution.
- Pain present for four days prior to hospitalization.
- Recently prescribed metronidazole (750 mg orally three times daily) for suspected bacterial cholecystitis.
- Patient self-discontinued antibiotic at onset of pain after three days of use (consumed 7.5 grams total).
- Clinical Examination:
  - Temp 99.0 F, P 135, RR 40, BP 137/66
  - Extreme pain and hypersensitivity present on palpation of hands and feet.
  - No sensation deficits or other neurological findings present.
  - No skin pallor, blistering, rash, or other skin abnormalities.
  - Labs significant for:
    - WBC: 22,000 cells/µL
    - Creatinine kinase 188 u/L
    - Lactate: 10.3 mmol/L
    - EMG: mixed axonal and demyelinating polyneuropathy of both ulnar nerves.

Diagnostic Approach

- A diagnosis of exclusion in the setting of known pre-exposure to an offending agent.
- Must exclude vitamin deficiencies, diabetes, trauma, autoimmune, and infectious sources.
- Nerve biopsy can be done in cases of uncertainty.
  - Biopsies show axonal demyelination and degeneration in the presence of neuropathic pain.

Management and Treatment

- Immediate: Aggressive pain management with intravenous fentanyl and ketamine.
- Acute: Pregabalin titration up to 450 mg/day, short course of intravenous ketorolac, and transition to oral narcotics (long and short acting).
- Long-term: Addition of imipramine, with titration to 50 mg/day, continued pregabalin, and weaned oral opioids over the following 2 months.
- Additional options: topical lidocaine or capsaicin ointment, tramadol, or venlafaxine.

Discussion

- Metronidazole-induced, long-nerve, painful neuropathy is an extremely rare side effect, and had previously occurred with doses between 12 and 228 grams.
- Interestingly, our patient received significantly less drug than other patients.
- Temperature anesthesia, decreased tactile sensation, autonomic neuropathy, and mild extremity neuropathy are more common neuropathies associated with the drug.
- Other associated drugs include isoniazid, dapsone, vinca alkaloids, taxane derivatives, amiodarone, digoxin, and cimetidine.
- Evaluate for axonal degeneration, demyelination, or nerve damage to aid in diagnosis.
- Etiology is currently idiopathic with some theories under investigation, including RNA synthesis inhibition or modulation of GABA sensitivity.
- Multiple pain management regimens have been trialed in patients presenting with these iatrogenic adverse events.
- Resolution of pain is dependent on nerve tissue healing; many patients only have partial resolution.

References