# Clinical Pharmacology & Toxicology Pearl of the Week

## Amiodarone – Part 2 – Neurotoxicity

The following is part of a series detailing specific organ toxicity of amiodarone, including basic information, diagnosis, and management.

**Case**

- A 75 year old male was started on amiodarone 200 mg per day in May because of ongoing atrial fibrillation episodes not controlled with bisoprolol. In conjunction with an electrical cardioversion, he has remained in normal sinus rhythm while on amiodarone 200 mg a day.

- In November, about one week after back surgery for spinal stenosis, he started to have gait ataxia and falls. These were not present in May/June when he was loaded with amiodarone. No other symptoms.

- Two months after onset of ataxia and falls, he was admitted to hospital. Repeat MRI showed no cord compression from the fall or any concerning post-surgical changes.

- Investigations:

    - Amiodarone concentration was 2.0 umol/L (N 2.0-4.0) in January, and 1.9 umol/L in February during his admission.

    - ALT was 23 in January. In February his ALT was 68 and AST was 47 (both elevated)

    - Multiple investigations confirmed evidence of demyelination as well as monoclonal gammopathy of unknown significance (MGUS), being treated with IVIG.

- Question: Could any of his symptoms be related to amiodarone neurotoxicity?

**Background**

- The overall incidence of amiodarone-induced neurotoxicity is thought to be around 2.8% in patients on average doses of 200 mg/day (range 100-400 mg/day).

- Initial reports of amiodarone neurotoxicity in the 1980s were likely dose-related as it was common to have patients on 600 mg a day, following 2 weeks of loading with 1600 mg/day.
    - The current recommendation of 200 mg/day dosing is a lower dose than those in initial reports, yet within the range that has been associated with neurotoxicity.
    - Review articles on amiodarone have included early and late reports of neurotoxicity rather than appropriately separating them based on daily dose

- A second risk factor is the loading dose period, where patients are loaded with 10-16 grams of amiodarone orally over several weeks.
    - Since amiodarone has sodium channel blockade as one of its therapeutic features, the thought is that it also inhibits neuronal sodium channels, leading to neurologic toxicity.

- A third risk factor is duration of therapy. Longer duration of amiodarone therapy is associated with a greater likelihood of neurotoxicity. In one study, the average duration of therapy was 31.6

months with a range of 2 weeks – 84 months. However, there were no amiodarone concentrations measured in this study.

**Clinical features**

- Neurotoxicity from amiodarone may present as any of the following clinical features:
  - Tremor is the most common manifestation (slowed nerve conduction).
  - Peripheral neuropathy, gait ataxia, cognitive impairment is also possible.
  - Other movement disorders, including Parkinsonism, myoclonus, and various dyskinesias have also been described.

**Management**

- Amiodarone has a very long elimination half-life of about 56 days and an elimination rate of 2% a day. Therefore, simply stopping the drug to observe for improvement in symptoms may require several months of observation.

- Reversal of symptoms once the amiodarone dose is stopped or reduced is not guaranteed. However, the majority of symptoms do improve with reduction of discontinuation of amiodarone.

**Case resolution**

- The recommendation was to decrease his weekly amiodarone dose to 1 gram by changing his dosing to 200 mg a day five days a week instead of every day.
  - In light of his amiodarone concentration of 2.0 umol/L in January, and the elevated ALT and AST in February, there was concern that he was starting to demonstrate features of amiodarone liver toxicity (which is often the first organ to show features of amiodarone toxicity)
  - Therefore, it made sense to reduce his dose, yet maintain the drug because of its effectiveness in controlling his atrial fibrillation

- His amiodarone blood concentrations will be followed once every 6 months to ensure they are in the 1.5 umol/L range (the effective concentration for management of atrial fibrillation).

- If reducing the dose does not improve his symptoms, and there is no improvement in neuro symptoms with IVIG, then we will consider switching to a different agent.

**The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. 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, and select option 1.**

**References**


1. Orr CF, Ahlskog JE. Frequency, characteristics, and risk factors for amiodarone neurotoxicity. Arch Neurol. 2009;66(7):865-869.
2. Epstein et al. Practical Management Guide for Clinicians Who Treat Patients with Amiodarone. Am J Med 2016; 129, 468-475.