Clinical Pharmacology & Toxicology Pearl of the Week

~Amiodarone – Part 2 – Neurotoxicity~

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

Case

- A 75-year-old male started receiving 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 taking amiodarone 200 mg a day.

- In November, about one week after back surgery for spinal stenosis, he started to experience gait ataxia and falls. These were not present when amiodarone was initiated six months earlier (approximately period of accumulation to steady state). 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-associated neurotoxicity is reported as 2.8% in patients on average doses of 200 mg/day (range 100-400 mg/day with unknown range of concentrations).

- 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 produces lower concentrations than those in initial reports, yet in some patients still within the range associated with neurotoxicity.
- Review articles on amiodarone have included early and late reports of neurotoxicity rather than appropriately separating them based on concentration or daily dose

- A second risk factor is the loading dose period, where patients may be rapidly 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. Concentration increases until steady state at 6 to 12 months. Thus, duration of 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 in the older population using this medication.

Management

- Amiodarone has an exceptionally long typical elimination half-life of about 56 days and an elimination rate of 1-2% 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 in serum concentration after reduced or discontinued amiodarone dosing.

Case resolution

- The recommendation was to decrease his total weekly amiodarone dose to 1000 mg taken as 200 mg a day five days a week.
    - 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 (often the first organ to show features of amiodarone toxicity)
    - Logically, reducing his dose would allow concentration to fall and yet maintain effectiveness in controlling his atrial fibrillation

- His serum amiodarone concentrations will be followed every 3 half-lives (6 months) targeting the 1.5 µmol/L range (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 use of a different, likely less effective agent, needs consideration.

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.

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, Specialist Link and through RAAPID. 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.

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