Clinical Pharmacology & Toxicology Pearl of the Week

~Amiodarone – Part 4 - Thyroid Toxicity~

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

Case:
A 78 y.o male receiving amiodarone develops a TSH < 0.01 and a free T4 of 41.1 pmol/L (normal range 10-25). You are consulted regarding approach and management of his condition.

This is a case of thyrotoxicosis associated with the excess iodine exposure present with amiodarone. It is often referred to as amiodarone-induced thyrotoxicosis (AIT) in the literature. AIT is classified into Types 1 and 2 based on the unproven hypothesis that amiodarone is directly toxic to thyroid tissue. Type I is due to excess iodine (typically seen earlier and in patients with pre-existing thyroid abnormalities: multinodular goiter or latent Graves' disease). Excess iodine then stimulates enhanced thyroid hormone production). Type II is hypothesised to be a destructive thyroiditis releasing pre-formed T4 and T3 and is typically seen much later (median 30 months) than type I. Evidence of direct toxicity is not strong and clear differentiation of Type I and Type II AIT may be difficult. Dedicated thyroid imaging studies may also be difficult because the high burden of iodine suppresses thyroid uptake. If there is evidence of local thyroid inflammation (pain, redness, heat, swelling) steroids are used.

Thyroid side-effects (of exposure to excess iodine from any source):

- ✓ Amiodarone has a high iodine content (6 mg of iodine associated with 200 mg of amiodarone is ~20 fold of the normal North American dietary intake).
- ✓ Amiodarone can stimulate both hypo- and hyperthyroidism.
- ✓ Excess iodine can cause hypothyroidism in about 10% of any population related to Wolff-Chaikoff effect (protective inhibition of thyroidal T4 and T3 production and release), while about 4% later develop hyperthyroidism from Jod-Basedow effect (increased iodine uptake, thyroid hormone synthesis, and thyroxine).
- ✓ Putatively, but poorly supported by studies, amiodarone is said to be directly toxicity to thyroid tissue (cell cultures are intoxicated when exposed to 100 times the clinically effective concentrations) and said to kill thyroid follicular cells, resulting in a destructive thyroiditis:
    - Amiodarone inhibits outer ring 5'-monodeiodination of thyroxine (T4), thus decreasing T3 production
    - Amiodarone and its desethylamiodarone metabolite reduce T3-receptor binding to nuclear receptor and decrease expression of some thyroid hormone-related genes.
- ✓ Changes in the pituitary hormone, TSH, frequently occur in euthyroid individuals treated with amiodarone. Monitoring free T4 and/or T3 is much more diagnostically useful than TSH. Trends in thyroid indices during amiodarone treatment in euthyroid patients are summarized below.

Table 1 Effects of amiodarone on thyroid function tests in euthyroid patients

	Duration of treatment	
Test	*Subacute (up to 3 months)*	*Chronic (> 3 months)*
T_4	Modest increase	Remains increased by up to 40% above baseline; may be in high reference range or modestly raised
T_3	Decreased, usually to low reference range	Remains in low reference range or slightly low
TSH	Transient increase (up to 20 mU/l)	Normal, but may be periods of high or low values
rT_3	Increased	Increased

From Newman et al. 1998

Table Pathogenesis and clinical features of amiodarone induced thyrotoxicosis

	Type I	*Type II*
Underlying thyroid abnormality	Yes	No
Pathogenetic mechanism	Excessive hormone synthesis due to iodine excess	Excessive release of preformed hormones due to thyroid destruction
Goitre	Multinodular or diffuse goitre normally present	Occasionally small, diffuse, firm, sometimes tender
Thyroidal radioiodine uptake	Normal/raised	Low/absent
Serum IL-6	Normal/slightly raised	Profoundly raised
Thyroid ultrasound	Nodular, hypoechoic, increased volume	Normal

From Newman et al. 1998

Management of amiodarone induced thyrotoxicosis:

- Neither amiodarone nor the iodine concentrations will decline quickly enough to help in the short term. If inflammation is documented, consider discontinuing amiodarone and starting steroids. However, alternative agents may not be effective. Therefore, inhibitors of iodine organification are generally needed.
- Type I
    - Antithyroid medications: methimazole favoured over PTU
    - Beta-blockade if amiodarone is not suppressing sympathetic response
    - Rarely thyroidectomy if refractory to medical management
- Type II
    - If inflammation is documentable, steroid administration with careful attention to tapering off.
    - Antithyroid medications still usually helpful.
    - Rarely thyroidectomy if refractory to medical management
- Mixed (typing is difficult): combination of above

Amiodarone induced hypothyroidism:

- Given there is no thyroid destruction, continue amiodarone and replace T4 (levothyroxine). Titrate dose and monitor Free T4 at 4-6 wk. intervals. TSH often remains above normal even though Free T4 has returned to upper limit of normal and patient is clinically euthyroid. TSH value of 4-10 is acceptable in this population. Trying to drive TSH below upper limit of normal despite normal thyroxine concentrations can lead to over-replacement.

- Amiodarone is usually not discontinued unless it fails to control the underlying arrhythmia. However, if amiodarone is stopped, hypothyroidism in patients with no apparent pre-existing thyroid disease sometimes resolves after body iodine normalizes in 6-12 months. However, hypothyroidism may persist after withdrawal of amiodarone in patients who have underlying chronic autoimmune thyroiditis with high titers of antithyroid peroxidase (TPO) antibodies and goiter and require permanent thyroxine replacement therapy.

Take Home Points:

- ✓ Remember that 10% of the population not receiving amiodarone require thyroid replacement.
- ✓ Amiodarone can be associated with both hypo- and hyperthyroidism from iodine excess.
- ✓ Treatment for amiodarone induced hypothyroidism typically involves thyroxine replacement without stopping amiodarone.
- ✓ Treatment for amiodarone-iodine-induced hyperthyroidism typically involves antithyroid medication, sometimes steroids, and very rarely thyroidectomy. Clinical experience suggests most patients respond to methimazole with a few months and it can be stopped.
- ✓ Alberta hyperthyroidism rate is greater than coastal provinces with higher background environmental iodine.

References:

1. Newman CM, Price A, Davies DW, Gray TA, Weetman AP. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart. 1998 Feb;79(2):121-7. doi: 10.1136/hrt.79.2.121. PMID: 9538302; PMCID: PMC1728611. https://heart.bmj.com/content/heartjnl/79/2/121.full.pdf
2. Ross DS. 2020 Jan. Amiodarone and thyroid dysfunction. . In J. A. Melin (Ed.), UpToDate. Retrieved June 7, 2021 from https://www.uptodate.com/contents/amiodarone-and-thyroid-dysfunction
3. Al Manasra T, Shah SQ, Raj SR, Pollak PT. Amiodarone Thyrotoxicosis: A Case of Pharmacy Error Obscured by Amiodarone Suppression of Symptoms of Highly Elevated Thyroxine Concentration. CJC Open. 2022 Dec 5;5(2):173-176. doi: 10.1016/j.cjco.2022.11.019. PMID: 36880080; PMCID: PMC9984889.

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.

More CPT Pearls of the Week can be found HERE.

Created: April 15, 2021

Reviewed: March 5, 2025