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, 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 amiodarone induced thyrotoxicosis. There are two types of amiodarone induced thyrotoxicosis. Type I is due to excess iodine (typically seen early on within a few months and in patients with pre-existing multinodular goiter or latent Graves' disease; the excess iodine from amiodarone provides increased substrate, resulting in enhanced thyroid hormone production). Type II is due to destructive thyroiditis (increased T4 and T3 release without increased production), and is typically seen much later (median 30 months) than type I. Type I and Type II amiodarone-induced thyrotoxicosis may be difficult to distinguish and involvement of experts with dedicated thyroid imaging studies may be helpful.

Thyroid side-effects:

- ✓ Amiodarone can cause both hypo- and hyperthyroidism.
- ✓ Amiodarone has high iodine content (6 mg of iodine associated with 200 mg of amiodarone is ~20 fold of the normal North American dietary intake).
- ✓ Excess iodine can cause hypothyroidism from Wolff-Chaikoff effect (protective inhibition of thyroidal T4 and T3 production and release) and hyperthyroidism/thyrotoxicosis from Jod-Basedow effect (opposite of Wolff-Chaikoff, increased thyroid hormone synthesis and release with excess iodine).
- ✓ Amiodarone also has intrinsic/direct toxicity to thyroid gland beside effects from excess iodine as it concentrates in the thyroid gland:
    - Amiodarone inhibits outer ring 5'-monodeiodination of thyroxine (T4), thus decreasing T3 production
    - Amiodarone (and its metabolite desethylamiodarone) blocks T3-receptro binding to nuclear receptor and decreases expression of some thyroid hormone-related genes.
    - Amiodarone has been suspected to have a direct toxic effect on thyroid follicular cells, which results in a destructive thyroiditis
- ✓ Transient changes in thyroid function tests frequently occur in euthyroid individuals treated with amiodarone. The changes in T4, T3, and TSH with respect to timing of amiodarone treatment in euthyroid patients are summarized in the table 1 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 3 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 for amiodarone induced thyrotoxicosis:

- Discontinue amiodarone if possible (for example, if alternative agent can be used for atrial fibrillation). However, neither amiodarone nor the iodine will decline quickly enough to help. Therefore inhibitors of thyroxine production or thyroid inflammation are generally needed.
- Type I
    - Antithyroid medications: PTU/Methimazole
    - Beta-blockade
    - +/- thyroidectomy if refractory to medical management and amiodarone cannot be stopped
- Type II
    - Steroid with careful attention to tapering off. Antithyroid medications often helpful.
    - +/- thyroidectomy if refractory to medical management and amiodarone cannot be stopped
- Mixed: combination of above

Amiodarone induced hypothyroidism:

- Typically, it is recommended to continue amiodarone and replace T4 (levothyroxine). Titrate dose and monitor Free T4 TSH at monthly intervals. TSH often remains above normal when Free T4 has returned to upper limit of normal and is clinically euthyroid. TSH 4-10 is acceptable in this situation as trying to drive TSH below 4 with other parameters normal 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 often resolves after body iodine normalizes in 6-12 months. In contrast, 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 they therefore require permanent T4 therapy

Take Home Points:

- ✓ Amiodarone can cause both hypo- and hyperthyroidism from iodine excess or direct toxicity.
- ✓ Treatment for amiodarone induced hypothyroidism typically involves replacement of T4 without stopping amiodarone. Ten percent of the population not receiving amiodarone require thyroid replacement.
- ✓ Treatment for amiodarone-induced hyperthyroidism depends on etiology (iodine excess or destructive thyroiditis or mixed). Treatment typically involves antithyroid medication, steroids, thyroidectomy or a combination of above. Clinical experience suggests most respond to methimazole.
- ✓ Alberta has a higher rate of hyperthyroidism than coastal provinces.

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. 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