

PHARMACOTHERAPY NEWSLETTER

Your source for unbiased, peer-reviewed answers to important patient care questions.

January 26, 2009

Volume 1; Issue 2

Podcast

Take Home Points

Setting Considerations

Counseling Points

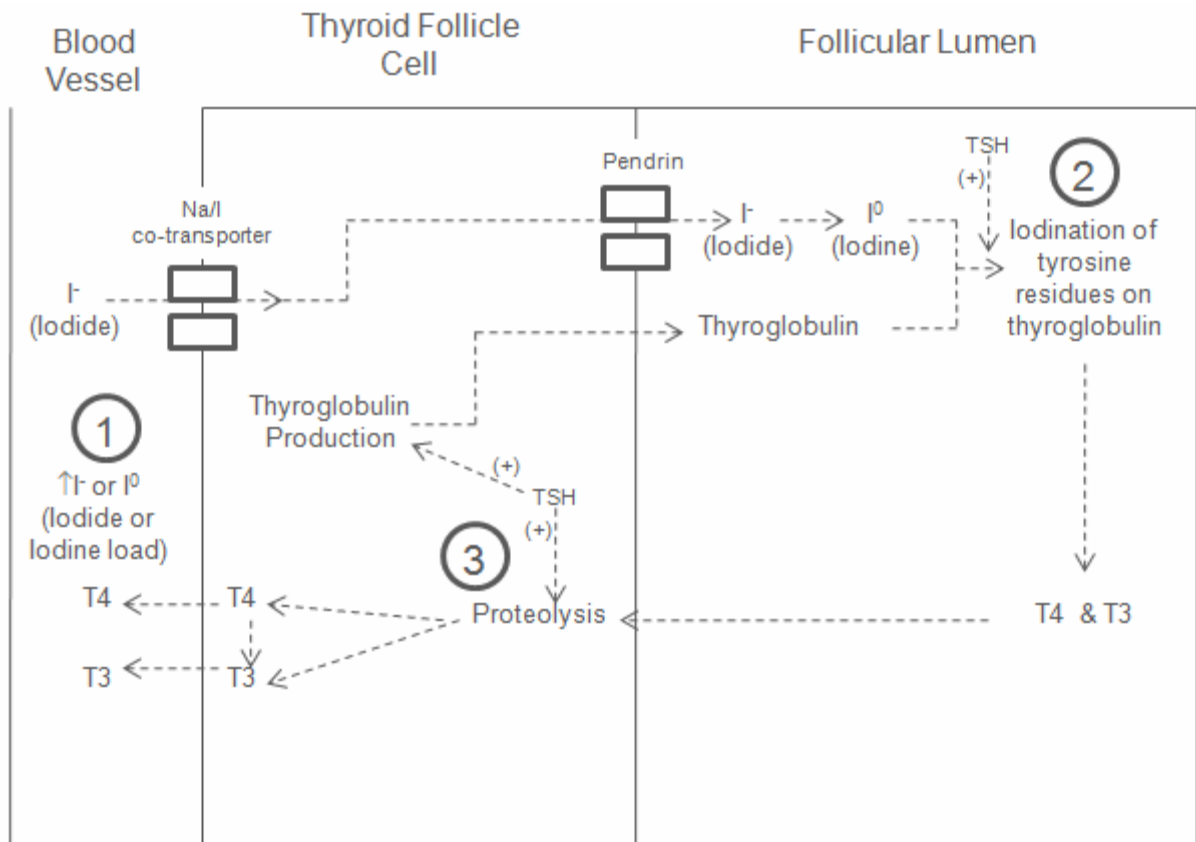
Legal Points

Take CE

Question: How can the oral antiarrhythmic medication, amiodarone (Cordarone®), cause hypothyroidism and is it relevant?

Answer: It is common to see some patients with high-risk or life-threatening ventricular arrhythmias and atrial fibrillation to be put on the antiarrhythmic, amiodarone (Cordarone®).^{1,2} When amiodarone is given to a euthyroid (normal thyroid function) patient, the normal physiologic process for the formation of the thyroid hormones, thyroxin (T4) and 3,5,3'-triiodothyronine (T3), can be affected. The following are the generalized steps of thyroid hormone production: thyroid releasing hormone (TRH) is secreted from the hypothalamus to stimulate the anterior pituitary gland to release thyroid stimulating hormone (TSH); the TSH then travels to the thyroid gland where it causes the increased production of thyroglobulin and the enzyme, thyroid peroxidase; iodide ingested from food or water enters into the thyroid follicular cell via the Na/I cotransporter; once the iodide is inside the thyroid follicle cell it is transported into the follicular lumen via the pendrin transporter. The iodide is oxidized by thyroid peroxidase into iodine where it then iodinates the tyrosine residues within the thyroglobulin to form both moniodotyrosine and diiodotyrosine, which then are used to make the T4 and T3; this newly produced T4 and T3 then undergo proteolysis and exocytosis for secretion and recycling. So then how does amiodarone affect this process?

Amiodarone's influence on the production and secretion of T4 and T3 occurs by several mechanisms. Most importantly, each 200 mg tablet of amiodarone contains 74.4 mg (37.3%) of iodine by weight with 10% (7.4mg) per day being released as free iodine.³ This is about a 50-fold greater amount than the daily recommended iodine intake which is known to be only 0.15 mg (150mcg) per day in adults.⁴ This increase in iodine concentrations is known to reduce blood flow into the thyroid gland (see 1 in diagram), inhibit the organification, or iodination, of the tyrosine residues on thyroglobulin molecule (see 2 in diagram), and decreases the release of thyroid hormones possibly due to an inhibition of thyroglobulin proteolysis (see 3 in diagram; last step in process for the release of T3 and T4).^{5,6} While not directly related to the development of hypothyroidism, amiodarone has been known to antagonize T3-induced gene expression at the tissue level which may play another role for amiodarone's effect in treating cardiac conditions.⁷ The combination of these events can result in sub-clinical and clinical hypothyroidism.^{2,8}



The incidence of amiodarone induced hypothyroidism has been reported to be as high as 10% of patients.^{1,2} Therefore, patients being started on amiodarone should have a baseline TSH determined and repeated at least yearly thereafter or based on the emergence of new symptoms of hypothyroidism. In patients with amiodarone-induced hypothyroidism, the TSH will be high and the free T4 levels will be low normal or low. If this occurs, it will usually be in the first 18 months of amiodarone initiation.⁹

(PW Pharmacother Newsl 2009;1(2):1-4.) ©2009 Pharmacology Weekly, Inc.

Take Home Points:

- Many patients with life-threatening ventricular arrhythmias or atrial fibrillation are put on the antiarrhythmic, amiodarone (Cordarone®),
- Each 200 mg tablet of amiodarone contains 74.4 mg (37.3%) of iodine with 10% (7.4 mg) per day being released as free iodine. This is about a 50-fold greater amount than the daily recommended iodine intake of 0.15mg.
- The increased iodine concentrations from amiodarone can reduce blood flow into the thyroid gland (see 1 in diagram); inhibit the organification, or iodination, of the tyrosine residues on thyroglobulin molecule (see 2 in diagram); and decrease the release of thyroid hormones, possibly due to an inhibition of thyroglobulin proteolysis (see 3 in diagram; last step in process for the release of T3 and T4).
- Patients being started on amiodarone should have a baseline TSH determined and repeated at least yearly thereafter or based on the emergence of new symptoms of hypothyroidism.

Considerations for Clinicians Based on Setting:

Outpatient Setting:

Encourage baseline assessment of thyroid function and monitor periodically thereafter or if the patient develops any signs or symptoms of hypothyroid states, since this can result in long-term complications with other organ systems.

Inpatient Setting:

If the patient is going to be started on amiodarone while in the hospital, encourage baseline assessment of thyroid function. If a hospitalized patient is receiving amiodarone, an assessment of thyroid function may be warranted based on reason for admission (e.g., any cardiac condition).

Important Counseling Bullet Point(s):

- Counsel patients on amiodarone about common signs and symptoms of hypothyroidism (bradycardia, heart failure, high cholesterol, weight gain, dry/cool skin, hair loss, fatigue, depression, etc.) and to tell their physician if they experience any of these, as there are tests that can help to determine thyroid function.

Medical/Legal Consideration(s):

- In *Crisp vs Bush*, No. 02-1272 (Circuit Ct., Boyd County, Ky. Sept. 27, 2005), a female patient sued three doctors, claiming all three were liable for the thyroid damage, vision loss, and pulmonary fibrosis she suffered due to post-operative administration of amiodarone.¹⁰ The patient's cardiologist first ordered the amiodarone following the patient's coronary artery bypass surgery, but the second cardiologist and internist did not alter the prescription after she later came under their care. The jury decided there was insufficient evidence that the doctors' negligence caused the patient's injuries, but the verdict in the case likely was simply due to the patient's weak expert testimony.¹⁰ Accordingly, whenever a patient is being administered amiodarone, it would be prudent to document thyroid function at baseline and then periodically thereafter.

Test Questions for CE:

Which of the following best represents the amount of iodine received with each 200 mg tablet of amiodarone?

- 74 mcg
- 150 mcg
- 74 mg
- 150 mg

Which of the following mechanisms accurately describes how amiodarone contributes to hypothyroidism?

- Increased proteolysis of T4 and T3
- Decrease in thyroglobulin production
- Decrease in blood flow to the thyroid gland
- Decrease delivery of iodine to the thyroid gland

Which of the following best describes the most common time frame for developing amiodarone induced hypothyroidism upon initiation in some patients?

- Within the first month only
- Within the first 3 months only
- Within the first 18 months
- It occurs at any time while on amiodarone

Pharmacology Weekly, Inc. is an accredited provider for continuing medical education (CME) by the American Academy of Continuing Medical Education (AACME) and this newsletter is worth 0.25 hours of category 1 CME for those subscribers with access to CE.

Medical Director: Gregory C. McKeever, MD

Editor-in-Chief: Anthony J. Busti, PharmD, BCPS, FAHA

Board Members & Reviewers: Jon Herrington, PharmD, BCPS, BCOP; Derek S. Lehew, PharmD; Brooke J. Daves, JD

Disclosures of Conflict of Interest: None

Issue Citation:

Busti AJ, Herrington JD, Lehew DS, Daves BJ, McKeever GC. How can the oral antiarrhythmic medication, amiodarone (Cordarone®), cause hypothyroidism and is it relevant? *PW Pharmacother News* 2009;1(2):1-4.

References:

1. Product insert. Amiodarone (Cordarone®) drug product insert. Wyeth Pharmaceuticals Inc. Philadelphia, PA. November 2008. Last accessed on 1/23/2009: <http://www.wyeth.com/products>
2. Batcher EL, Tang XL, Singh BN et al. Thyroid function abnormalities during amiodarone therapy for persistent atrial fibrillation. *Am J Med* 2007;120:880-5. [PubMed](#)

3. Rao RH, McCready VR, Spathis GS Iodine kinetic studies during amiodarone treatment. *J Clin Endocrinol Metab* 1986;62:563-8. [PubMed](#)
4. United States Department of Agriculture (USDA). Dietary reference intakes: elements. Last accessed on 1/23/2009. [USDA - Element Table](#)
5. Becker DV, Braverman LE, Dunn JT et al: The use of iodine as a thyroidal blocking agent in the event of a reactor accident: Report of the Environmental Hazards Committee of the American Thyroid Association. *JAMA* 1984;252:659-61. [PubMed](#)
6. Erbil Y, Ozluk y, Giris M et al. Effect of lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. *J Clin Endocrinol Metab* 2007;92:2182-9. [PubMed](#)
7. Norman MF, Lavin TN. Antagonism of thyroid hormone action by amiodarone in rat pituitary tumor cells. *J Clin Invest* 1989;83:306-13. [PubMed](#)
8. Martino E, Safran M, Aghini-Lombardi F et al. Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. *Ann Intern Med* 1984;101:28-34. [PubMed](#)
9. Trip MD, Wiersinga W, Plomp TA. Incidence, predictability, and pathogenesis of amiodarone-induced thyrotoxicosis and hypothyroidism. *Am J Med* 1991;91:507-11. [PubMed](#)
10. Patterson RM, Hoyle PC, Editorial Staff of the Publishers of Lawyers' Medical Cyclopeda eds. *Drugs in Litigation: Damage Awards Involving Prescription and Nonprescription Drugs*. 2008 Edition. LexisNexis. San Francisco, CA.

©2009 Pharmacology Weekly, Inc.
P.O. Box 719
Salado, Texas 76571
www.pharmacologyweekly.com

All rights reserved. Pharmacology Weekly, Inc. is a Texas corporation, advised by healthcare providers who provide unbiased education regarding the relevance of pharmacology in generally accepted practices. This newsletter is sent out to active subscribers weekly, and any and all use of this newsletter is subject to the Terms and Conditions of Pharmacology Weekly, as set forth on the [pharmacologyweekly.com](http://www.pharmacologyweekly.com) website. If you are receiving this newsletter without a subscription, such transmission to you is in violation of such Terms and Conditions, and the sender could be subject to civil liability for such violation of Pharmacology Weekly's intellectual property rights. Please notify Pharmacology Weekly immediately of such person's violation of the Terms and Conditions. You, too, may be subject to such civil liability should you continue to receive such newsletters without purchasing a subscription or should you forward this newsletter to someone else.

No part of this material may be reproduced, stored, or transmitted in any way whatsoever without written permission from the President of Pharmacology Weekly. The editors rely primarily on peer-reviewed, published medical information and on the opinions of the editorial staff and independent peer-reviewers. All education and recommendations are considered to be educational and not meant to apply to specific patients. The above information should be used appropriately in the context of the provider's legal role as a healthcare provider in their respective state or country. Pharmacology Weekly does not accept responsibility for the application of this information in direct or indirect patient care. It is the responsibility of the healthcare provider to ascertain the Food and Drug Administration status of each drug and to check the product information provided by the manufacturer of each drug for any changes. The editors and authors have made every effort to provide accurate and complete information and shall not be held responsible for any damage from any error, possible omission, or inaccuracy. To the extent this newsletter provides information on legal issues, it is not intended to provide advice on any specific legal matter or factual situation. This information is not intended to create, and receipt of it does not constitute, an attorney-client relationship. Readers should not act upon this information without seeking professional legal counsel.



www.pharmacologyweekly.com