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Editorial commentary: Amiodarone-induced thyroid diseases: Additional unintended consequences

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Amiodarone is the most widely prescribed antiarrhythmic agent and is among the top 200 most widely prescribed drugs in the United States, with more than 3 million prescriptions written in 2015 [1]. Amiodarone has long been considered the most effective of the antiarrhythmic agents for a variety of arrhythmias, including maintenance of sinus rhythm for patients with paroxysmal and persistent atrial fibrillation (AF) [2–4], facilitation of resuscitation of ventricular fibrillation [5,6], and reducing the frequency of shocks in patients with implantable cardioverter-defibrillators [7]. Unfortunately, however, amiodarone is associated with an alarming adverse effect profile [8]. Among the most complex adverse effects associated with amiodarone are those associated with the thyroid. Amiodarone may induce hypothyroidism or hyperthyroidism; this apparent dichotomy has been the source of confusion for many clinicians. How can amiodarone cause opposing effects on the thyroid gland in different patients?

In the current issue of the journal, Trohman et al. [9] provide an extensive review of thyroid disease associated with amiodarone therapy. Their review covers mechanisms of both hypo-and hyperthyroidism associated with amiodarone and helps to resolve the dichotomy of amiodarone's seemingly contradictory effects on the thyroid. The authors also discuss myriad clinical manifestations of thyroid diseases induced by amiodarone. Supplemental to Trohman and colleagues' review, there are additional and potentially unexpected consequences of amiodarone-induced thyroid diseases that warrant discussion. Specifically, amiodarone-associated thyroid diseases may exacerbate specific drug interactions known to be precipitated by this antiarrhythmic drug.

As Trohman et al. discuss briefly in their review [9], hyperthyroidism and particularly thyrotoxicosis, regardless of the etiology, enhance sensitivity to the anticoagulant effects of warfarin, which, despite the availability of non-vitamin K antagonist oral anticoagulants (NOACs), remains one of the most commonly prescribed anticoagulant agents [1]. The pharmacokinetic interaction between amiodarone and warfarin is well-known; amiodarone enhances warfarin-induced anticoagulation primarily via inhibition of cytochrome P450 2C9 [10], increasing the risk of warfarin-associated bleeding. In patients taking amiodarone and warfarin concomitantly who develop amiodarone-induced thyrotoxicosis, this bleeding risk is further enhanced. Thyrotoxicosis augments warfarin-associated suppression of clotting factors II and VII, and increases the rate of degradation of clotting factors, accelerating their clearance from plasma and reducing their half-lives [11]. These mechanisms have manifested in pronounced elevations in international normalized ratio (INR) in patients taking warfarin who have developed amiodarone-induced thyrotoxicosis [11–13], further increasing the risk of bleeding associated with the combination of amiodarone and warfarin. Clinicians caring for patients taking amiodarone and warfarin concomitantly should be aware of the potential for marked elevations in INR in patients who develop amiodarone-induced thyrotoxicosis, and must be prepared to heighten INR monitoring, and, where appropriate, adjust warfarin dose or substitute an alternate anticoagulant agent until a euthyroid state is restored.

Another drug interaction that can be exacerbated via the influence of amiodarone on thyroid function is that of amiodarone

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and digoxin. While not recommended as a first-line agent for rate control in patients with AF, digoxin remains a commonly used drug in patients with AF who also have heart failure, as it is one of the few ventricular rate control medications that does not possess negative inotropic activity [14]. Digoxin is a substrate of the drug transporter p-glycoprotein (P-gp), while amiodarone is a potent P-gp inhibitor [15]. Consequently, amiodarone increases mean serum digoxin concentrations by more than two-fold during concomitant administration [16]. Thyroid disease, specifically hypothyroidism, adds to this risk. Hypothyroidism suppresses the expression of p-glycoprotein, resulting in reduced digoxin clearance, with minimal influence on bioavailability or volume of distribution [16]. As a result, serum digoxin concentrations are increased up to 35% in patients with hypothyroidism [16]. While a 35% increase in serum digoxin concentration alone may not be clinically significant in many patients, an additional increase of that magnitude added to increased digoxin concentrations owing to the pharmacokinetic interaction between amiodarone and digoxin is not desirable. Moreover, hypothyroidism also alters the response to digoxin, increasing the likelihood of digoxin toxicity [17]. Therefore, amiodarone-induced hypothyroidism may have additional unanticipated effects on serum digoxin concentrations and response beyond that which may be expected to be attributable solely to the pharmacokinetic interaction between amiodarone and digoxin.

Inhibition of P-gp also may increase serum concentrations of, and risk of bleeding associated with the NOACs apixaban, dabigatran, edoxaban, and rivaroxaban [15]. Further, P-gp inhibition may increase serum concentrations of other drugs that may be used concomitantly with amiodarone, including diltiazem, verapamil, labetalol, losartan, nadolol, propranolol, atorvastatin and lovastatin [15]. In view of the influence of hypothyroidism on P-gp expression, it seems reasonable to assume that there is an increased risk of adverse effects associated with these and other P-gp substrates in patients who develop amiodarone-induced hypothyroidism beyond the risk anticipated due to amiodarone's P-gp inhibition alone.

Trohman and colleagues [9] have provided a welcome and thorough review of mechanisms, clinical manifestations, and treatment of thyroid diseases associated with amiodarone. Clinicians should be aware of the fact that amiodarone-associated thyroid diseases have the potential to exacerbate the magnitude of well-known drug interactions associated with this antiarrhythmic drug.

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