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INVITED COMMENTARY

Towards an animal model of amiodarone-induced thyroid dysfunction

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The drug amiodarone, originally introduced in clinical medicine in 1962 for the treatment of angina pectoris, continues to arouse interest among cardiologists and thyroidologists. To the cardiologist amiodarone is one of the most potent antiarrhythmic agents in the management of cardiac tachyarrhythmias refractory to other treatment modalities. In recent years amiodarone has also been applied successfully in the treatment of severe congestive heart failure and in the prevention of sudden death in patients with cardiomyopathy. Amiodarone as a class III antiarrhythmic agent prolongs the duration of the action potential in cardiac tissue; it also decreases heart rate and myocardial oxygen consumption. These actions are quite similar to those observed in hypothyroid patients, leading to the hypothesis that one of the mechanisms of action of amiodarone is the induction of a local hypothyroid-like condition in the heart (1). Amiodarone may thus act as a thyroid hormone antagonist, and this view is supported by the finding that desethylamiodarone – the main metabolite of amiodarone – inhibits the binding of tri-iodothyronine (T_3) to its nuclear receptors *in vitro* at concentrations within the range observed during amiodarone treatment *in vivo* (2). The curiosity of thyroidologists is further enhanced by the clinical experience that amiodarone may induce either hypothyroidism or thyrotoxicosis. Indeed, it can be said that once we understand the pleiomorphic effects of amiodarone on thyroid hormones, we will have a precise knowledge of the mechanisms of thyroid hormone regulation, secretion, metabolism and mechanism of action. The effects of amiodarone on thyroid hormones can be divided into facultative changes (amiodarone-induced hypothyroidism and amiodarone-induced thyrotoxicosis) occurring in some but not all patients, and obligatory changes observed in every subject treated with amiodarone.

The obligatory changes affect both the thyroid gland and extrathyroidal tissues. The obligatory thyroidal effects are due to iodine excess generated by the drug. Amiodarone contains 39.33% iodine by weight, and large quantities of iodide are released during biotransformation of the drug. In a study of 15 patients taking 300 mg amiodarone daily for 6 months, plasma inorganic iodide and 24-h urinary iodide rose 40-fold

at 6 weeks and remained at these high levels thereafter (3). The thyroid gland adapts to these pharmacological quantities of iodide by decreasing thyroid hormone synthesis and thyroid hormone release (the former is known as the Wolff-Chaikoff effect). As a consequence, serum thyrotrophin (TSH) slightly increases in the first three months of amiodarone treatment. The thyroid gland, however, usually escapes from the inhibitory effects of iodine excess, and serum TSH returns to baseline values. The obligatory extrathyroidal effects of amiodarone are related to inhibition of iodothyronine-5'-deiodination, which is partly secondary to inhibition of thyroxine (T_4) transport across the plasma membrane. It results in altered kinetics of thyroid hormones: the production rate of T_3 decreases, whereas the metabolic clearance rates of T_4 and reverse (r) T_3 decrease. This explains the characteristic changes of thyroid function tests in patients on long-term amiodarone treatment: low serum T_3 and high serum rT_3 , T_4 and free T_4 concentrations with normal TSH values (4).

In contrast to these obligatory changes, amiodarone-induced hypothyroidism (AIH) and amiodarone-induced thyrotoxicosis (AIT) occur only in a subset of patients. Interestingly, AIH is observed more frequently in females and in iodine-replete areas, whereas AIT is more prevalent in males and in iodine-deplete areas (5, 6). In view of the differences in geographic and sex distribution, one is tempted to question how these determinants are involved in the pathogenesis of AIH and AIT. Several studies have shed more light on this difficult issue. AIH is apparently caused by a failure of the thyroid gland to escape from the Wolff-Chaikoff effect, resulting in permanent inhibition of organification. This is more likely to happen in subjects with pre-existent autoimmune thyroiditis. Indeed, the presence of antibodies against thyroid peroxidase (TPO) prior to treatment constitutes a relative risk of 7.3 for the subsequent development of AIH (6). The prevalence of autoimmune thyroiditis is relatively high in areas with a high environmental iodine intake and in females; these are precisely the factors which predispose to AIH. The situation is more complex with regard to the pathogenesis of AIT. AIT shares several characteristics with iodide-induced thyrotoxicosis: it is more common in males, the onset is often acute, and it is

more prevalent in iodine-deficient regions. The latter may be related to the sensitivity of the thyroid gland to generate an iodine-induced turn-off signal for hormone synthesis, which is increased in subjects accustomed to a high environmental iodine intake. In iodine-deplete areas, this sensitivity may be diminished and iodine excess may unmask existing thyroid autonomy in euthyroid patients with Graves' disease or nodular goitre. Excessive thyroid hormone synthesis induced by iodine excess thus seems the pathogenetic mechanism of AIT in patients with an underlying thyroid abnormality, known as AIT type I. However, AIT also occurs in patients without any evidence of pre-existent thyroid disease, and this has been labelled AIT type II. In contrast to AIT type I, AIT type II is characterized by a low or suppressed thyroidal radioiodine uptake, markedly elevated serum interleukin-6 concentrations and the frequent occurrence of a subsequent hypothyroid stage. These phenomena are reminiscent of subacute thyroiditis. It has therefore been proposed that the pathogenetic mechanism of AIT type II is excessive thyroid hormone release caused by destructive thyroiditis (7). Destruction of thyroid tissue might be induced by the iodine excess *per se*, by amiodarone or its metabolites themselves, or by both.

It is against this background that the paper of Pitsiavas *et al.* in this issue of the Journal is of much interest (8). They studied ultrastructural changes in the thyroid gland of rats treated with amiodarone or with a comparable amount of sodium iodide. The experiments were carried out in normal Wistar rats, and in BB/W rats who are prone to autoimmune thyroiditis. When starting to read their paper, I was curious to find out if amiodarone *per se* would cause greater thyroid damage than iodine excess alone, if the occurrence of AIT would be observed at all, and indeed if the BB/W rat would be susceptible to the development of AIH. How far did the paper meet my expectations?

From the results of Pitsiavas *et al.* (8) it is clear that amiodarone treatment causes extensive damage to the thyroid gland far beyond that caused by equivalent doses of iodide. Amiodarone disrupts the architecture of the thyroid both at a cellular and subcellular level, and it is easy to visualize how amiodarone causes destructive thyroiditis. The findings thus support the proposed pathogenesis of AIT type II, and are in line with several other studies. In primary cultures of human thyroid follicles amiodarone is cytotoxic at concentrations of $\geq 48 \mu\text{g/ml}$; the cytotoxic effect of potassium iodide requires a 4-fold higher concentration on a molar base (9). Desethylamiodarone (DEA) is more cytotoxic for human thyrocytes in culture than amiodarone itself; the EC_{50} value of DEA is $6.8 \pm 1.1 \mu\text{g/ml}$ (10). The concentrations found to be cytotoxic *in vitro* are of the same order as those actually observed in amiodarone-treated patients (amiodarone and DEA concentrations are $14 \mu\text{g}$ and $64 \mu\text{g}$ per gram thyroid tissue respectively) (11). The cytotoxic effect of amiodarone on

human thyrocytes occurs independently of the effects on iodide organification (9) – in contrast to that of high iodide doses which can be prevented by inhibition of organification (12) – suggesting that thyroid cytotoxicity by amiodarone is a direct effect of the drug on thyrocytes; excess iodide released from the drug may contribute to its toxic action.

The ultrastructural changes observed by Pitsiavas *et al.* (8) in their rat model might also provide a clue to the nature of amiodarone-induced cytotoxicity. Amiodarone as an amphiphilic drug has a strong attraction for intralysosomal phospholipids, and the binding of the drug and these phospholipids renders them indigestible by phospholipases. The bound complexes form the intralysosomal multilamellar inclusion bodies, which have been found in many organs of patients treated with amiodarone (13). It results in a rising tissue-to-plasma drug ratio with increasing duration of treatment. Disruption of subcellular organelle function seems to explain the toxic effects of amiodarone; it is in line with the clinical observation that toxicity increases with time and for some manifestations is related to the total cumulative dose of amiodarone (14).

As indicated by Pitsiavas *et al.* (8), their histopathological findings are akin to the severe follicular damage and disruption in surgical specimens of patients who underwent thyroidectomy because of AIT type II (15). As specimens from amiodarone-treated euthyroid patients reveal minimal or no thyroid follicular damage (16), one would expect some degree of thyrotoxicosis in the amiodarone-treated rats with marked follicular disruption. This was, however, not observed. On the contrary, serum TSH was slightly increased as compared with controls, to the same extent as in the iodine-treated animals. This might be indicative of the continued presence of the inhibiting effects of iodine excess on thyroid hormone synthesis and release. It is further notable that amiodarone treatment did not result in an increase in serum T_4 or a decrease in serum T_3 ; in fact, the only biochemical evidence that amiodarone had been administered was the increase in serum rT_3 . This suggests that tissue accumulation of amiodarone and DEA was still limited. One wonders if a higher cumulative dose of amiodarone will eventually result in thyrotoxicosis. This can be tested by prolongation of the duration of treatment and/or increasing the daily dose of amiodarone. Sequential measurements of serum TSH and free T_4 would be helpful in such experiments, as well as the determination of tissue contents of amiodarone and DEA. One might even try by putting the rats on an iodine-deficient diet to increase the incidence of AIT type II. The outcome of this kind of experiment might have clinical relevance in explaining why most patients remain clinically euthyroid (probability 0.56) but will develop a suppressed TSH (probability 0.72) at some time during amiodarone therapy (figures calculated for 4 years of treatment) (6). Patients with a suppressed TSH

have a high probability of a spontaneous return to a normal TSH despite continuation of amiodarone treatment (6). The implication is that the transient presence of a suppressed TSH in euthyroid patients may represent an asymptomatic episode of amiodarone-induced destructive thyroiditis. In view of the gradual accumulation of amiodarone and DEA in tissues, the cytotoxic effect of amiodarone and DEA on thyrocytes will be expressed only when intrathyroidal drug concentrations exceed a certain threshold level. In support of this reasoning is the observation that the TSH response to thyrotrophin-releasing hormone decreases in a dose-dependent manner with increasing cumulative doses of amiodarone (17). One may speculate that the clinically silent destructive thyroiditis may lower the intrathyroidal drug concentration, allowing the repair phase to proceed uninterrupted.

The amiodarone-induced thyroidal changes reported in the paper by Pitsiavas *et al.* (8) were qualitatively similar although quantitatively slightly amplified in the BB/W rats relative to the Wistar rats. Amiodarone-induced hypothyroidism did not occur. The choice of the BB/W rat seems to be appropriate since normal humans and rats are relatively resistant to the effects of iodine excess. An excess of dietary iodine accelerates the development of thyroid autoimmunity in the BB rat (a risk factor for AIH in humans), but they remain euthyroid (18). Although most BB/W rats do develop lymphocytic thyroiditis, TPO-antibodies have not been convincingly demonstrated in these animals and hypothyroidism does not occur. One could argue that the obese strain chicken – another model for Hashimoto disease but with spontaneous development of TPO-antibodies and hypothyroidism (19) – would be a more suitable experimental animal model for the induction of AIH.

In summary, the paper by Pitsiavas *et al.* (8) has provided new evidence for a direct cytotoxic effect of amiodarone on the thyroid gland, which is different from that of iodine excess. Their findings are relevant for our understanding of the pathogenesis of AIT type II. Furthermore, they have shown the way for further experiments which will be needed to explain satisfactorily the Janus' face of amiodarone being capable of inducing either thyrotoxicosis or hypothyroidism.

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