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CORRESPONDENCE

Research Correspondence

Risk of Potentially Life-Threatening Thyroid Dysfunction Due to Amiodarone in Idiopathic Pulmonary Arterial Hypertension Patients

To the Editor: Amiodarone is used as an antiarrhythmic agent in patients with pulmonary hypertension, who suffer the double insult of having an increased susceptibility to arrhythmias as well as being more likely to suffer cardiovascular compromise as a result of these arrhythmias (1). Other agents, e.g., beta-blockers, may be unsuitable due to their negative inotropic effect. Thyroid dysfunction is a well-known side effect of amiodarone, with a prevalence of up to 24% in patients with acquired heart disease (2). We noted that a disproportionately high number of patients with idiopathic pulmonary arterial hypertension (IPAH) suffered from amiodarone-induced thyroid dysfunction (AITD) with severe consequences. Therefore, we decided to study amiodarone use and thyroid function in pulmonary hypertension.

We examined all IPAH patients diagnosed from 1995 to 2007 (n = 120), and identified patients on amiodarone for ≥3 months (n = 21), and patients who had never been on amiodarone (n = 72). Controls were chosen from patients with chronic thromboembolic pulmonary hypertension (CTEPH) (n = 23) on amiodarone for ≥3 months; and PAH associated with congenital heart disease (CHD) (n = 12) on amiodarone for ≥3 months. Three months was chosen as the minimum, as transient increases in TSH (thyroid-stimulating hormone) are common after introduction of amiodarone, and the pituitary-thyroid axis normally stabilizes after 3 months (2). Details are available in the Online Appendix. Approval was obtained from the local ethics committee.

The IPAH patients on amiodarone were younger than CTEPH and CHD controls. They had a higher mean pulmonary artery pressure compared with CTEPH (49 ± 9 mm Hg vs. 41 ± 13 mm Hg, $p < 0.05$), but not compared with CHD (54 ± 24 mm Hg). There were no differences in cardiac index, pulmonary vascular resistance, or amiodarone exposure between IPAH and CTEPH groups. Exposure to amiodarone was standardized to "200 mg/day/year" units (dose-years). CHD patients had the greatest exposure to amiodarone (3.8 ± 2.6 dose-years vs. 2.4 ± 2.5 dose-years [IPAH] vs. 1.5 ± 1.4 dose-years [CTEPH], $p = 0.01$).

Twelve of the 21 (57.1%) IPAH patients on amiodarone developed thyroid dysfunction, compared with 12 of 72 (16.7%) of IPAH patients not on amiodarone ($p < 0.001$).

The IPAH group treated with amiodarone was 3.4 (1.8 to 6.5) times more likely to develop thyroid dysfunction than IPAH patients not on amiodarone. The prevalence of AITD in IPAH was also significantly elevated compared with the prevalence of AITD in CTEPH (57.1% vs. 17.4%, $p = 0.01$). The IPAH group on amiodarone was 3.3 (1.3 to 8.6) times more likely to develop thyroid dysfunction than CTEPH patients on amiodarone. Of the 12 IPAH patients who developed AITD, 8 required hospitalization and 2 died. One CHD and 2 CTEPH patients needed hospitalization, and there were no deaths.

We then compared the characteristics of all patients who developed AITD with all patients who remained euthyroid (Fig. 1). There was an overrepresentation of IPAH in AITD (64% vs. 20%, $p = 0.003$). There was a trend towards greater amiodarone exposure in all patients who developed AITD compared with those that did not (2.6 vs. 1.7 dose-years, $p = 0.06$). IPAH patients with AITD had a greater exposure to amiodarone compared with IPAH patients on amiodarone who remained euthyroid (2.8 vs. 0.7 dose-years; $p = 0.008$). There was a trend towards significance in the equivalent CTEPH groups (2.8 vs. 1.5 dose-years; $p = 0.08$).

IPAH patients have a higher prevalence of thyroid disease than the general population, estimated at 19% to 24% (3) compared with a baseline of 2.5% to 9.5% (4). The exact reasons for this remain unclear, but may be related to an autoimmune component in the pathobiology of IPAH (5). Thyroid dysfunction is a well-known side effect of amiodarone. However, we noted that the prevalence of AITD in CTEPH was 17%, which is in keeping with the prevalence of AITD in left heart disease. Therefore, we infer that the presence of pulmonary hypertension per se does not increase the risk of AITD, but rather the presence of *idiopathic* pulmonary hypertension.

This increase in AITD is also not simply attributable to prolonged use of amiodarone in a predominantly female population; as the CHD patients have a greater exposure but a lower prevalence of AITD. A possible underlying explanation is that amiodarone is unmasking a tendency towards autoimmune thyroid disease in IPAH. Amiodarone can have a direct cytotoxic effect on thyroid follicular cells (6). This would release previously hidden antigens and may enable sensitization to occur in vulnerable IPAH patients. Unfortunately, we were not able to compare the type of autoantibodies present in the PAH cohorts as investigation of thyroid disease was left to referring hospitals.

The main drawback of this study was its predominantly retrospective nature, which inevitably resulted in missing data. These were filled by consulting referring physicians. The other problem lies in the small numbers, which is due to the rarity of these diseases and the selection of subgroups. After taking statistical advice, we have not attempted to perform multivariate analysis.

The other striking result is that in IPAH, the extent of exposure to amiodarone may matter. Should a true dose-dependent relationship exist, strategies that could be implemented include avoiding amiodarone altogether or resorting to amiodarone as a short-term measure, prior to radiofrequency ablation. Should ablation prove impossible, another alternative to amiodarone would be its iodine-free derivative dronedarone, which has very few thyroid side effects.

This investigation demonstrates that IPAH patients are particularly susceptible to AITD, with potentially life-threatening consequences. Prolonged exposure increases the risk. Chronic amiodarone should only be prescribed after careful consideration of all other options. IPAH patients who are on amiodarone should have their

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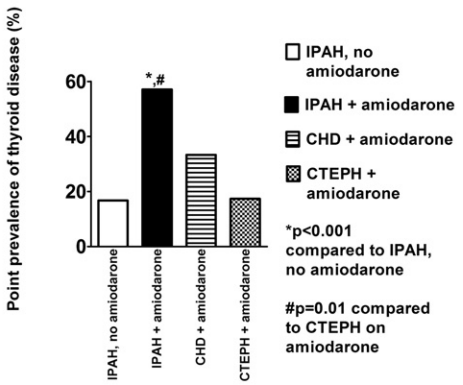

B

Parameter	PAH on amiodarone with AITD	PAH on amiodarone, euthyroid	p-value
Age on starting amiodarone, years	48.2 (16.6)	56.4 (16.2)	0.078
% female	64%	60%	1.000
% IPAH	64%	20%	0.003
mPAP, mmHg	49.2 (15.3)	43.2 (15.1)	0.200
CI, $Lmin^{-1}m^{-2}$	2.2 (0.7)	2.0 (0.5)	0.330
PVR, Wood units	10.5 (6.2)	10.4 (6.4)	0.960
Dose of amiodarone, mg/day	169 (41)	180 (35)	0.400
Duration on amiodarone, years	3.3 (2.3)	2.0 (1.9)	0.057
"200mg/day/year" units	2.6 (1.9)	1.7 (1.4)	0.059

Figure 1 **Prevalence of Thyroid Disease and Associated Risk Factors in PAH**

(A) Point prevalence of amiodarone-induced thyroid disease in all pulmonary arterial hypertension (PAH) groups; and **(B)** comparison of PAH patients who developed amiodarone-induced thyroid dysfunction (AITD) and who remained euthyroid on amiodarone. Data shown as mean (SD). CHD = congenital heart disease; CI = cardiac index; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.

thyroid function monitored closely and be treated aggressively should they develop AITD.

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Key Words: amiodarone ■ pulmonary hypertension ■ thyroid.

APPENDIX

For an expanded Methods section, please see the online version of this article.