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ORIGINAL REPORT

Amiodarone-induced thyroid dysfunction associated with cumulative dose

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SUMMARY

Purpose To obtain risk estimates of thyroid disorder in patients starting amiodarone.
Methods We followed a cohort of 5522 patients with a first prescription for an anti-arrhythmic drug and no previous use of thyroid drugs. Within this cohort we conducted a nested case–control analysis. Cases were defined as all patients who started a thyreomimetic or thyreostatic drug no sooner than 3 months after the start of an anti-arrhythmic drug. Controls were patients with a comparable follow-up period not receiving any thyroid drugs during the observation period.
Results We identified 123 cases who had started thyreostatic drugs and 96 cases who had started a thyreomimetic drug. In users of amiodarone we found an adjusted odds ratio of 6.3 (3.9–10.2) for hyperthyroidism and 6.6 (3.9–11.1) for hypothyroid disease compared to users of other antiarrhythmics. Patients who were exposed to a cumulative dose exceeding 144 g of amiodarone had an adjusted odds ratio of 12.9 (6.1–27.3) for the development of hyperthyroid disease. The dose response for development of hypothyroidism was less pronounced.
Conclusions We observed an increased risk for thyroid disorder at the high end of that reported in the literature. The risk of thyroid disorder increased with exposure to higher cumulative doses. Clinicians should keep in mind the possibility of development of thyroid disorders in patients on treatment with amiodarone even after several years of use.

KEY WORDS — amiodarone; hypothyroidism; hyperthyroidism; adverse drug reactions

INTRODUCTION

Due to aging of the population and decreased cardiovascular mortality in patients with acute coronary artery disease the incidence of both congestive heart failure and arrhythmias is increasing.[1–3] Sudden death is the major cause of death in patients with congestive heart failure and is frequently associated with (ventricular) arrhythmias.

Since class I antiarrhythmic drugs have proarrhythmic effects and increase mortality, amiodarone or implantable cardioverter defibrillators (ICD) are the preferred treatment for ventricular arrhythmias. Amiodarone is considered less likely to give rise to secondary arrhythmias and may be especially beneficial in patients with advanced heart failure and rapid resting heart rates. Patients with refractory atrial fibrillation and ventricular arrhythmias in particular, are frequently treated with amiodarone.[4] Approximately 10% of patients with congestive heart failure receive treatment with amiodarone.[5]

However several serious side-effects such as pneumonitis, skin reactions, liver function abnormalities and thyroid disorders have been reported after

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exposure to amiodarone.[6] These toxic effects seem to be related to the total dose of amiodarone administered.[7] Alterations in thyroid hormone metabolism during treatment with amiodarone have been reported for many years.[8] Thyroid disorders may occur in patients with pre-existing thyroid abnormalities and in subjects with apparently normal thyroid glands.[9] Several mechanisms for amiodarone-induced thyroid dysfunction are postulated. Amiodarone is structurally related to thyroid hormones and can inhibit the conversion of thyroxine to triiodothyronine. Each molecule of amiodarone contains two atoms of iodine. Because of this high iodine content, amiodarone can inhibit thyroid hormone synthesis and secretion. Conversely, particularly in regions with a low intake of iodine (e.g. the Netherlands and most European countries) this high iodine content of amiodarone also leads to excessive thyroid hormone synthesis and subsequent hyperthyroidism. Inflammation is an alternative etiologic mechanism for the development of hyperthyroidism.[10]

Data on the incidence of amiodarone-induced thyroid disorders are conflicting. An incidence between 4 and 20% is reported.[11–13] This variability in risk probably arises from several factors such as the duration of treatment and the cumulative dose of amiodarone. Different estimates of the risk of amiodarone-induced thyroid disorders could also arise from the fact that some studies counted all patients with elevated levels of thyroid hormones, while other studies only counted patients with clinical manifestations of thyroid disorder. This study aims to obtain reliable risk estimates on amiodarone-induced thyroid disorders in a large cohort of patients with a long follow-up period.

PATIENTS AND METHODS

Patients and data

Data were retrieved from the PHARMO record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of six medium-sized cities in the Netherlands.[14] Medication histories were collected from 1986 to 1999. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification.

We selected a cohort of 17 228 patients with at least one prescription for an antiarrhythmic drug (ATC-code C01AA01-C01AX99 (digoxin and related drugs), C01BA01-C01BX99 (other antiarrhythmics) or C07AA07 (sotalol)). Patients with a follow-up of less than 1 year, less than 180 days use of antiarrhytmics and a history of thyreostatic or thyreomimetic drugs in the year before the start of the antiarrhythmic drug were excluded from the cohort. The remaining study cohort consisted of 5522 patients representing 21 730 person-years of follow-up (mean follow-up period 3.9 years). Within this cohort a nested case–control analysis was performed.

Cases and controls

Patients receiving a prescription for a thyreostatic drug (carbimazole, thiamazole or propylthiouracil) with or without a simultaneous or succeeding prescription for a thyreomimetic drug, were considered to be treated for hyperthyroidism. Patients receiving a thyreomimetic drug (levothyroxine or triiodothyronine) without a simultaneous or preceding thyreostatic drug were considered to be treated for hypothyroid disorder. Patients, within the cohort of patients receiving antiarrhythmics, who did not receive any thyroid drugs served as controls. The date of the start of a thyreostatic or thyreomimetic drug was the index date of the cases. We assigned an index date to controls comparable to the calculated average time in the follow-up of the cases.

Exposure definition

A patient was defined as a current user when there was at least one prescription for amiodarone filled in the 3 months before the start of the use of a thyroid drug. To assess the presence of a dose–response relationship we calculated the total amount of amiodarone dispensed to the patient before the start of a thyroid drug. The average maintenance dose of amiodarone was 200 mg. We therefore categorized exposure into less than 72 g (less than 360 tablets of 200 mg; i.e. approximately 1 year of use), between 72 and 144 g (between 360 and 720 tablets of 200 mg; i.e. between 1 and 2 years of use) and more than 144 g (more than 720 tablets of 200 mg; i.e. more than 2 years of regular use).

Data analysis

We performed a nested case–control analysis comparing exposure in cases versus controls. Odds ratios were calculated for exposure to amiodarone before the start of the use of a thyroid drug (cases) or matched index date (controls). We calculated odds ratios both for current and prior use of amiodarone. Multivariate unconditional logistic regression analysis

was performed to adjust for potential confounders such as age, sex and antiarrhythmic co-medication.

Kaplan–Meier survival curves were plotted to show the percentage of amiodarone-treated patients in whom treatment for either hyperthyroid or hypothyroid disease was initiated as a function of time.

All statistical analyses were performed with Egret (Egret for windows, version 2.0, Cytel Software Corporation) and SPSS (SPSS for windows, version 10.0, SPSS Inc.) software.

RESULTS

In the cohort of 5522 patients exposed to any antiarrhythmic drug we identified 123 cases who had started thyreostatic drugs (carbimazole, thiamazole or propylthiouracil with or without a thyreomimetic drug) and 96 cases who had started a thyreomimetic drug (levothyroxine or triiodothyronine, without a thyreostatic drug).

Hyperthyroid disease

The use of amiodarone was associated with an increased risk for hyperthyroidism; crude odds ratio 4.9 (CI 95% 3.0–7.8), adjusted odds ratio 6.3 (CI 95% 3.4–8.4). In patients who were exposed to more than 144 g (720 doses of 200 mg) the adjusted odds ratio was 12.9 (6.1–27.3) (Table 1). Almost 13% of patients had developed hyperthyroidism 3.5 years after initiation of amiodarone therapy. Most patients develop hyperthyroidism between 2 and 3 years after the start of amiodarone (Figure 1).

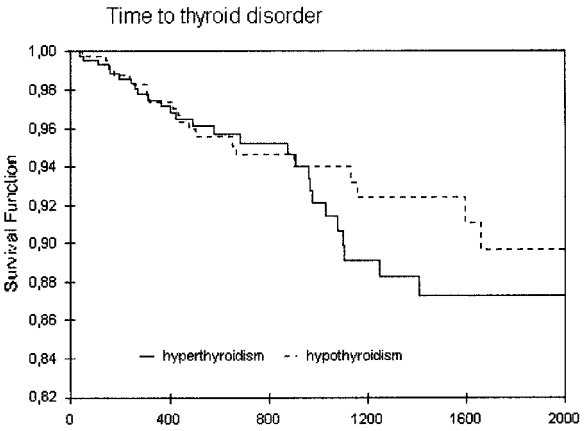

Figure 1. Development of thyroid disorder during follow-up

Since the incidence of hyperthyroid disease is higher for women, we stratified for gender (Table 1). The crude odds ratios for men and women were comparable, although slightly higher in men than women (6.8 vs. 4.6). However we did not find a dose–response relationship in women and a very clear dose–response relationship in men (Table 1).

Table 1. Association between use of amiodarone and risk of hyperthyroid dysfunction

	Cases ($N = 123$)		Controls ($N = 5303$)		Crude OR	Adjusted OR*
	N	%	*N*	%		
Current use of amiodarone	24	19.5	250	4.7	4.9 (3.0–7.8)	6.3 (3.9–10.2)
Prior use of amiodarone	28	22.8	328	6.2	4.5 (2.8–7.1)	5.4 (3.4–8.4)
Total use < 72 g	10	8.1	171	3.2	3.1 (1.5–6.3)	3.4 (1.7–6.8)
Total use 72–144 g	8	6.5	100	1.9	4.2 (1.8–9.2)	4.9 (2.2–10.5)
Total use > 144 g	10	8.1	57	1.1	9.2 (4.3–19.3)	12.9 (6.1–27.3)
Stratified for gender						
Female	88	71.5	2559	48.3		
Current use of amiodarone	11	12.5	78	3.0	4.5 (2.2–9.2)	4.8 (2.4–9.5)
Prior use of amiodarone	15	17.0	109	4.3	4.6 (2.4–8.6)	4.9 (2.7–8.9)
Total use < 72 g	7	8.0	58	2.3	4.0 (1.6–9.6)	4.0 (1.8–9.2)
Total use 72–144 g	6	6.8	34	1.3	5.9 (2.2–15.3)	6.7 (2.6–16.9)
Total use > 144 g	2	2.3	17	0.7	3.9 (0.6–18.3)	4.4 (1.0–19.9)
Male	35	28.5	2744	51.7	0.4 (0.2–0.6)	0.3 (0.2–0.5)
Current use of amiodarone	13	37.1	172	6.3	8.8 (4.1–18.7)	8.2 (4.0–16.9)
Prior use of amiodarone	13	37.1	219	8.0	6.8 (3.2–14.4)	6.2 (3.0–12.6)
Total use < 72 g	3	8.6	113	4.1	2.7 (0.7–10.9)	2.7 (0.8–9.2)
Total use 72–144 g	2	5.7	66	2.5	3.5 (0.6–15.7)	3.5 (0.8–15.5)
Total use > 144 g	8	22.9	40	1.5	20.6 (8.8–58.4)	20.7 (8.4–51.2)

*Adjustment was made by multivariate logistic regression. Model contained gender, age, prior use of digoxin, sotalol, or any other antiarrhythmic.

Table 2. Association between use of amiodarone and risk of hypothyroid dysfunction

	Cases ($N = 96$)		Controls ($N = 5303$)		Crude OR	Adjusted OR*
	N	%	*N*	%		
Current use of amiodarone	21	21.9	249	4.7	5.7 (3.4–9.4)	6.6 (3.9–11.1)
Prior use of amiodarone	23	23.9	336	6.3	4.7 (2.9–7.5)	5.0 (3.0–8.3)
Total use < 72 g	7	7.3	163	3.1	2.9 (1.2–6.4)	3.2 (1.4–7.1)
Total use 72–144 g	10	10.4	97	1.8	6.9 (3.5–13.8)	8.5 (4.2–17.5)
Total use > 144 g	5	5.2	74	1.4	4.5 (1.8–11.5)	4.8 (1.9–12.5)
Stratified for gender						
Female	66	68.8	2559	48.3		
Current use of amiodarone	11		83		6.0 (2.8–12.3)	6.3 (3.2–12.7)
Prior use of amiodarone	12	18.2	114	4.5	4.8 (2.3–9.5)	5.0 (2.6–9.8)
Total use < 72 g	4	6.1	59	2.3	3.1 (0.9–9.2)	3.4 (1.2–9.7)
Total use 72–144 g	6	9.1	27	1.1	10.1 (3.6–27.0)	10.6 (4.1–27.4)
Total use > 144 g	2	3.0	28	1.1	3.2 (0.5–14.5)	3.3 (0.8–14.4)
Male	30	31.3	2744	51.7	0.4 (0.3–0.7)	0.3 (0.2–0.5)
Current use of amiodarone	10		166		7.8 (3.3–17.8)	7.4 (3.4–16.5)
Prior use of amiodarone	10	33.3	220	8.0	5.7 (2.5–13.1)	6.0 (2.8–13.0)
Total use < 72 g	3	10.0	104	3.8	3.6 (0.8–13.2)	3.2 (0.9–10.9)
Total use 72–144 g	4	13.3	70	2.6	7.2 (2.0–23.1)	7.0 (2.3–21.4)
Total use > 144 g	3	10.0	46	1.7	8.2 (1.9–30.7)	7.6 (2.1–27.0)

*Adjustment was made by multivariate logistic regression. Model contained gender, age, prior use of digoxin, sotalol, or any other antiarrhythmic.

Hypothyroidism

The use of amiodarone was associated with an increased risk for hypothyroidism as well; crude odds ratio 5.7 (CI 95% 3.4–9.4), adjusted odds ratio 6.6 (CI 95% 3.9–11.1). Unlike the development of hyperthyroidism we could not find a clear association between total exposure to amiodarone (in grams) and the risk for developing hypothyroid disease (Table 2). Approximately 10% of patients had developed hypothyroidism 4 years after the initiation of amiodarone therapy. Most patients develop hypothyroidism within 2 years (Figure 1).

Since the incidence of hyperthyroid disease is higher for women, we stratified for gender (Table 2). The crude odds ratios for men and women were comparable, although slightly higher in men than women (7.4 vs. 6.3). The data showed a tendency to develop hypothyroid disease at higher exposures in men (Table 2).

DISCUSSION

In this study we found an increased risk of 6.3 (3.9–10.2) for hyperthyroidism and 6.6 (3.9–11.1) for hypothyroid disease comparing current users of amiodarone with users of other antiarrhythmics. Moreover, the results show a very clear relationship between the total exposure to amiodarone and the development of hyperthyroid disorder.

Although conventional pharmacological therapy (synthetic (anti)thyroid drugs) is not always effective in amiodarone-induced thyroid disease, all patients will initially be treated with pharmacotherapy.[15] So this should not underestimate the presented risk. The use of these drugs as an indicator of hyper- or hypothyroid disease therefore seems appropriate. However since amiodarone-induced thyroid disorders can be subclinical and will not always be recognized, this study only reports on cases who are treated for thyroid disorders. We could therefore still have underestimated the risk for thyroid disorders.

Thyroid disorders are more frequent in females than males.[16] Arrhythmias on the other hand are more frequent in men than women. Gender could therefore be an important confounder. The relation between thyroid disorders and age is less clear. Yet the relation between age and arrhythmias is definite. Both gender and age have therefore been included in our logistic regression.

Previous research suggested that female sex was a risk factor for development of thyroid disorder in users of amiodarone.[17] It is generally known that female gender is a risk factor for thyroid disease.[16] Stratification showed that risk estimates for thyroid disorder for men and women were comparable. This suggests that

although women have a higher baseline risk of thyroid disorder, the relative risk when using amiodarone is not higher in women. Furthermore it is interesting to note that women tend to develop thyroid disorder when they are exposed to lower total doses of amiodarone than men. This could imply either that women are more sensitive to developing thyroid disorder or that doses given to women are relatively higher than those administered to men. This warrants research into differential dosing of amiodarone in both sexes.

Arrhythmias such as atrial fibrillation can be secondary to a thyroid disorder. It is not uncommon to find that arrhythmias for which patients are treated primarily, arise from a thyroid disorder.[10] This would lead to increased risk estimates when comparing the risk of thyroid disorder in patients receiving amiodarone with patients not receiving antiarrhythmic drugs. We therefore restricted our study to a cohort of patients treated with antiarrhythmics.

Since this is a non-randomized study the possibility of confounding by indication should be examined. Apart from including potential confounders in a multivariate model, we explored this possibility by calculating odds ratios for several other antiarrhythmics prescribed in our cohort. We did not find any increased risk of thyroid disorders in users of other antiarrhythmics except an association between the use of digoxin and hyperthyroid disease (adjusted odds ratio of 1.7, CI 95% 1.1–2.5). In our view this moderate increase in risk may indeed be due to confounding by indication. We are supported in this by the fact that we did not find an association between the total exposure to digoxin and the development of hyperthyroid disease as we observed for the use of amiodarone (Table 1). This type of confounding will probably not apply to amiodarone, since this drug is not prescribed as first line therapy in patients presenting with arrhythmias.

Another source for potential confounding is co-medication which has been linked to thyroid disorders. Best documented are thyroid disorders due to use of lithium, interferon and iodine-containing X-ray contrast liquids. We did not include the use of this co-medication in our logistic regression since the use of these drugs is not frequent in our population.

In daily practice two strategies in patients receiving long-term amiodarone seem appropriate: either regular control of serum thyroid hormone levels at least twice a year or continuous monitoring for clinical symptoms of thyroid disorder. Withdrawal of amiodarone could be considered when thyroid disorders occur. In many cases continuation of therapy will be preferable. Amiodarone-induced hypothyroidism is treated with levothyroxine and hyperthyroidism with anti-thyroid drugs. Thyroidectomy is an option in the case of resistance to treatment with anti-thyroid drugs. Thyroidectomy can also be considered when continued use of amiodarone is desired. The study shows an incidence of thyroid disease that is at the higher end of the scales reported in earlier literature studies. This is probably related to the relative long follow-up period. In our opinion our study may even underestimate the absolute risk of amiodaron-related thyroid disorder.

KEY POINTS

- Thyroid disorders during use of amiodarone are common
- Thyroid disorders occur up to 4 years after starting of amiodarone
- Start of thyreostatic or thyreomimetic drugs can be used as a marker for the occurrence of thyroid disorders
- Thyroid disorders occur more frequently in females than males but relative risks during use of amiodarone are comparable
- Females may develop thyroid disorders earlier then men

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