Magnitude and time course of urinary iodine excretion in relation to thyroid function in patients on amiodarone therapy

Giuseppe Pinto (✉ pintogiuseppe.pg@gmail.com)  
San Raffaele Institute: IRCCS Ospedale San Raffaele  https://orcid.org/0000-0003-2213-2955

Giulia Marchionni  
San Raffaele Institute: IRCCS Ospedale San Raffaele

Massimo Locatelli  
San Raffaele Institute: IRCCS Ospedale San Raffaele

Luca Foppoli  
San Raffaele Institute: IRCCS Ospedale San Raffaele

Giuseppe Monaca  
San Raffaele Institute: IRCCS Ospedale San Raffaele

Gabriele Fragasso  
San Raffaele Institute: IRCCS Ospedale San Raffaele  https://orcid.org/0000-0003-2022-774X

Research Article

Keywords: amiodarone, urinary, iodine, thyrotoxicosis, hypothyroidism, cardiac arrhythmias

Posted Date: March 23rd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2701321/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Purpose.** Amiodarone is a source of excess iodine that may induce thyroid dysfunction. The aim of the present analysis was to evaluate the magnitude and time course of 24-hr urinary iodine excretion and its potential relationship with thyroid disorders in patients on antiarrhythmic prophylaxis with amiodarone.

**Methods.** 24-hr urinary iodine excretion and thyroid function were evaluated in 67 patients on chronic amiodarone therapy. All patients were clinically and biochemically euthyroid before starting treatment and were followed up by 6-month measurements of 24-hr urinary iodine excretion and plasma TSH levels.

**Results.** Since amiodarone initiation, 20 patients developed thyroid dysfunction (14 hypothyroidism, 3 subclinical hypothyroidism, 3 hyperthyroidism). No differences were observed in terms of treatment length or urinary iodine levels between patients remaining euthyroid and those developing thyroid dysfunction: urinary iodine in the euthyroid group was 8094 µg/24h (IQR 4082-10766) vs 10851 µg/24h (IQR 8529-12804) in the thyroid dysfunction group at 6 months (p = 0.176) and 8651 µg/24h (IQR 6924-11574) vs 8551 µg/24h (IQR 4916-13580) (p = 0.886) at one year from amiodarone initiation. The occurrence of thyroid dysfunction was equally distributed among patients taking amiodarone for more than one year versus those under treatment for less than one year. Upon amiodarone withdrawal, normal range of urinary iodine was achieved after a mean time of 15.2 ± 7.7 months.

**Conclusion.** These results suggest no correlation between 24-hr urinary iodine excretion and thyroid dysfunction in patients on amiodarone therapy. Thyroid disorders following amiodarone administration likely depend on the individual predisposition to iodine load.

Introduction

Amiodarone is a benzofuranic, iodine-rich drug, extensively used in the management of supraventricular and ventricular arrhythmias, usually administered at a daily dose of 200 mg [1]. Each 200 mg tablet contains about 75 mg of iodine (37% by weight), of which approximately 15% is released as free iodine after deiodination. Administration of this drug can increase plasma inorganic iodide up to 40-fold and urinary iodide excretion of at least 15000 µg per 24h [2]. The central role of iodide in thyroid physiology has been known for many years. The iodine atoms constitute 65% and 59% of T4 and T3 by weight respectively, and - as extensively demonstrated in previous studies - both iodine excess and deficiency strongly predispose to the development of thyroid dysfunction [3]. Around 15–20% of amiodarone-treated patients develop either thyrotoxicosis (AIT) or hypothyroidism (AIH), that can arise either early or late during treatment and in apparently normal thyroid glands or in the presence of underlying thyroid pathologies [4, 5]. AIH seems to be more common in iodine-replete areas, while AIT more likely occurs in iodine-deficient areas [6–9]. Predisposing risk factors, besides the pre-existing thyroid disorders (nodular goitre, latent Graves’ disease, chronic autoimmune thyroiditis, positivity for thyroid-specific antibodies), are still unknown and the underlying pathophysiological mechanisms poorly understood [6, 10]. Amiodarone is a highly lipid-soluble molecule concentrated mostly in adipose tissue, muscles, liver, lungs
and thyroid gland. The half-life of amiodarone is highly variable, ranging from 50 to 100 days. Its stored fraction may provide excess of iodine for months after the last dose is administered, leading to increased iodine stores for up to 9 months after discontinuation of the therapy [10, 11]. Since the majority of iodine absorbed by the body is excreted in urine, urinary iodine (UI) is considered a sensitive marker of current iodine intake and daily UI excretion (24-hr urinary iodine) is considered to be an accurate measurement [12]. In this study we have evaluated the relationship between 24-hr urinary iodine excretion and treatment length in relation to the occurrence of thyroid disorders in patients on antiarrhythmic prophylaxis with amiodarone. Additionally, we evaluated urinary iodine wash-out rate after amiodarone discontinuation.

Patients And Methods

From the cohort of patients attending the Heart Failure Clinic at San Raffaele Hospital, we studied 67 patients (52 males, median age 73 years; IQR 65–79) who started amiodarone administration (200 mg once a day) for management of supraventricular or ventricular arrhythmias and who were not taking any drug or supplement known to affect thyroid hormone metabolism or iodine intake. The whole study population was clinically and biochemically euthyroid before treatment initiation. 24h-urinary iodine and thyroid hormones, thyroid stimulating hormone (TSH) and free thyroxine (fT4) were evaluated at baseline and at each cardiological evaluation at 4–6 month intervals after amiodarone initiation. In case of amiodarone discontinuation, 24h-urinary iodine levels were continued to be monitored until their return to baseline values. Urinary iodine was evaluated as 24hr-urinary iodine excretion and determined through the standard Sandell-Kolthoff spectrophotometric method, while thyroid hormones were essayed through ELISA technique.

Hypothyroidism was defined as a serum TSH ≥ 10 mU/L. Subclinical hypothyroidism was defined as a serum TSH between 4 and 10 mU/L with normal levels of fT4. Hyperthyroidism was defined as a serum TSH < 0.05 mU/L, either with or without fT3 and fT4 elevation.

Ethical approval of the study was obtained from the Ethic Committee of the San Raffaele Hospital (IODURIA-2/int/2020).

Statistical analysis. Pati ents data were extrapolated from patients clinical charts and collected on an Excel file (Microsoft Corporation, Redmond, WA, USA). Statistical analysis was performed using Prism (GraphPad Software, San Diego, Ca, USA). Given the nature of urinary iodine values, we used – as suggested by previous studies [12, 13] – the median as the preferential statistical tool to describe the distribution of our values among the different data sets. We compared the median values of urinary iodine in different groups using the Mann-Whitney test; the alpha level was set at a conventional 0.05. Reference values for normal 24h-urinary iodine excretion are reported in Table 1.
Table 1
Reference values for normal 24h-urinary iodine excretion

<table>
<thead>
<tr>
<th>AGE</th>
<th>NORMAL 24H-URINARY IODINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–17 YEARS</td>
<td>Not established</td>
</tr>
<tr>
<td>≥ 18 YEARS</td>
<td>75–851 µg/24 hour</td>
</tr>
</tbody>
</table>

Results

Of the 67 patients under study, 20 (30%) developed thyroid dysfunction at 38 ± 33 months following amiodarone administration. Of these patients, 14 (70%) developed overt hypothyroidism, 3 subclinical hypothyroidism (15%) and 3 (15%) hyperthyroidism. In patients developing thyroid dysfunction, amiodarone was withdrawn soon after. Table 2 shows the occurrence of different thyroid abnormalities in the thyroid dysfunction group and their gender-related distribution.

<table>
<thead>
<tr>
<th>Occurrence of the different thyroid abnormalities in the thyroid dysfunction group and gender-related distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Subclinical Hypothyroidism</td>
</tr>
</tbody>
</table>

Treatment duration was less than 1 year (8 ± 6 months) in 50% of the individuals developing thyroid disorders. The remaining 50% had been on amiodarone for more than 1 year (67 ± 30 months). Apart from the 20 individuals who developed thyroid abnormalities during amiodarone administration, 15 additional individuals discontinued treatment with this agent for thyroid-unrelated reasons (poor control of arrhythmic events, poor tolerability, absence of continuing need for antiarrhythmic prophylaxis). Overall, of the 35 patients that terminated treatment, mean amiodarone therapy duration was 32 ± 24 months. In this group, upon amiodarone withdrawal, return to normal range of urinary iodine was achieved after a mean time of 15 ± 7 months. No statistically significant difference was detected in urinary iodine levels between patients remaining euthyroid and those developing thyroid dysfunction (8094 µg/24h [IQR 4082–10766] vs 10851 µg/24h [IQR 8529–12804] at 6 months [p = 0.176] and 8651 µg/24h [IQR 6924–11574] vs 8551 µg/24h [IQR 4916–13580] at 1 year from amiodarone initiation [p = 0.886]) (Table 3, Fig. 1).
Table 3
Urinary iodine excretion at 6 months and 1 year from amiodarone initiation

<table>
<thead>
<tr>
<th></th>
<th>Dysthyroidism</th>
<th>Euthyroidism</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>10851 µg/24h</td>
<td>8094 µg/24h</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>(8529–12804)</td>
<td>(4082–10766)</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>8551 µg/24h</td>
<td>8651 µg/24h</td>
<td>0.886</td>
</tr>
<tr>
<td></td>
<td>(4916–13580)</td>
<td>(6924–11574)</td>
<td></td>
</tr>
</tbody>
</table>

Urinary iodine levels were available for the entire study population at 6 months from amiodarone initiation (20 patients in the group who developed dysthyroidism and 47 patients in the euthyroid group) and for fewer patients at 1 year because of amiodarone discontinuation (11 patients in the group who developed dysthyroidism and 37 patients in the euthyroid group).

When considering patients who terminated treatment with amiodarone, no remarkable differences were detected in the levels of urinary iodine after discontinuation of the drug between patients developing thyroid dysfunction and those maintaining the euthyroid state. In fact, no statistically significant differences were observed in terms of urinary iodine levels at 4 months, 6 months or 1 year from amiodarone withdrawal. To compare the clearance of urinary iodine after amiodarone withdrawal we considered the time points better represented in the population under study. In Table 4 urinary iodine excretion levels (µg/24h) after amiodarone withdrawal at 4 months, 6 months and 1 year are reported. While we observed a progressive decrease of urinary iodine levels in patients maintaining the euthyroid state who needed to stop amiodarone therapy for thyroid-unrelated reasons, a different trend of the curve of iodine excretion was noted in patients who stopped amiodarone because of thyroid dysfunction, with an initial slight increase of urinary iodine levels at 4 months despite amiodarone discontinuation. A graphic representation of this trend is displayed in Fig. 2.

Table 4
24h-urinary iodine excretion levels after amiodarone withdrawal at 4 months, 6 months and 1 year

<table>
<thead>
<tr>
<th></th>
<th>Dysthyroidism</th>
<th>Euthyroidism</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months</td>
<td>3339 µg/24h</td>
<td>6244 µg/24h</td>
<td>0.165</td>
</tr>
<tr>
<td></td>
<td>(2156–5746)</td>
<td>(4187–8577)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>4870 µg/24h</td>
<td>1291 µg/24h</td>
<td>0.258</td>
</tr>
<tr>
<td></td>
<td>(2998–5894)</td>
<td>(692–2355)</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>542 µg/24h</td>
<td>439 µg/24h</td>
<td>0.731</td>
</tr>
<tr>
<td></td>
<td>(107–821)</td>
<td>(111–733)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

The results of the present study show the lack of correlation between the magnitude of 24-hr urinary iodine excretion - expression of body iodine load and metabolism - and thyroid dysfunction in patients on amiodarone treatment. In fact, no substantial difference in 24h-urinary iodine excretion between euthyroid patients compared to those developing thyroid dysfunction was detected. Additionally, a threshold beyond which thyroid disorders develop more frequently could not be evidenced; this characteristic was maintained when considering urinary iodine levels at 6 months and 1 year from therapy initiation. Nonetheless, the results of this study confirm the greater risk of thyroid disorders in patients on amiodarone therapy. As previously demonstrated in other studies, hypothyroidism is the most common thyroid disorder secondary to amiodarone administration in iodine-replete areas [2, 7]. However, persistent thyroid hormones abnormalities have been consistently found in euthyroid patients receiving long-term amiodarone treatment [14]. It has been postulated that amiodarone-induced hypothyroidism may arise from failure to escape the Wolff-Chaikoff effect and consequent permanent iodine-induced inhibition of thyroid hormone synthesis, with or without development of autoimmune thyroiditis [6, 15]. Amiodarone-induced thyrotoxicosis (AIT) is classified as type 1 or type 2. Type 1 AIT occurs in patients with underlying thyroid pathology such as autonomous nodular goitre or Graves’ disease. Type 2 AIT is a result of amiodarone causing a destructive thyroiditis with release of preformed thyroid hormones into the circulation [16, 17]. A younger age, male gender, thyroid autoantibody production, goitre, and low body mass index are associated with amiodarone-induced hyperthyroidism [6, 10, 15–16], while an older age, higher baseline thyroid-stimulating hormone (TSH) level, lower left ventricular ejection fraction, diabetes mellitus, and thyroid autoantibody production in women are possible risk factors for amiodarone-induced hypothyroidism [6, 7, 10, 17–19]. Dilated cardiomyopathy and cardiac sarcoidosis have also been indicated as independent risk factors for the development of amiodarone-induced hyperthyroidism [20].

Our study was conducted on a homogeneous population of euthyroid patients, apparently free from any thyroid disorder before treatment initiation. Within this population we confirmed that, in agreement with other studies, excessive iodine load secondary to amiodarone intake and length of administration are not predisposing factors for the development of thyroid disorders. In fact, the occurrence of thyroid dysfunction was equally distributed among patients on amiodarone for more than one year versus those under treatment for less than one year, indicating that the development of thyroid dysfunction is probably independent from the duration of amiodarone-induced excessive iodine load. Given the characteristics of the studied population, it is possible to assume that vulnerability to thyroid diseases in patients on amiodarone therapy is probably more related to individual predisposition and individual genetic background. This assumption is concordant with the well-recognized central role of autoantibodies in the pathogenesis of both AIH and AIT and with studies demonstrating particular HLA correlations with amiodarone-induced thyroid dysfunction [21]. However, in different populations, the magnitude of urinary iodine has been associated to both high [22] and low [23] prevalence of thyroid autoantibodies.

After amiodarone withdrawal, compared to patients developing either hypothyroidism or hyperthyroidism, a faster normalization of urinary iodine levels was observed in individuals maintaining a normal thyroid
function. This observation might be related to different kinetics of urinary iodine excretion in the two
groups or merely on the inter-individual variability of different patients. Nonetheless, the majority of
patients that terminated treatment achieved normalization of urinary iodine levels at around one year
from amiodarone withdrawal, independently from the amount of urinary iodine at the time at which
therapy was discontinued. In some cases, iodine excess has been shown to persist up to 2 years after
amiodarone discontinuation, where obesity with high drug accumulation in the adipose tissue could be
the likely cause [24]. This aspect is of particular interest when considering patients requiring treatment
with radioactive iodine, since iodine excess prevents uptake of the iodine based radioisotope, thus
preventing the diagnostic and therapeutic benefit deriving from its use. Where necessary, in patient with
high-risk differentiated thyroid cancer, iodine excess could be rapidly lowered by plasma exchange,
thereby allowing radioactive iodine ablative therapy [24–25]. These issues suggest that, in association
with thyroid hormones, the presence of thyroid autoantibodies should be routinely evaluated before the
initiation of amiodarone treatment. A recent study has evidenced an association between increased
iodine intake and autoimmune thyroiditis, indicating that excessive iodine intake may trigger thyroid
autoimmunity and eventually thyroid dysfunction [26]. Finally, identification of gene polymorphisms [27–
28] associated with development of amiodarone-induced adverse events could also be potentially useful
to personalize treatment and eventually avoid – whenever possible – exposure to this antiarrhythmic
agent in individuals more likely to develop thyroid dysfunction.

Study limitations. The observational nature of this analysis is the first and main limitation. As this study
was carried out in a single center and the sample size was small, generalizability of these results is
limited. A prospective study with a larger sample size, including the evaluation of thyroid autoantibodies
as well, is warranted to further validate our observations.

Conclusion

The present study shows no correlation between 24-urinary iodine excretion, as a measure of total iodine
load and metabolism, and development of thyroid disorders in patients on antiarrhythmic prophylaxis
with amiodarone. Iodine clearance after amiodarone discontinuation is quite slow, with normalization of
urinary iodine levels after around one year from the last exposure to this agent. This issue is of particular
relevance when considering patients requiring treatment with radioactive iodine, since iodine excess
prevents uptake of the iodine based radioisotope, thus preventing the diagnostic and therapeutic benefit
deriving from its use. Based on these results, it is reasonable to assume that development of thyroid
disorders secondary to amiodarone therapy results from an individual predisposition which cannot be
detected by looking at the iodine status but that should be probably related to individual susceptibility to
the massive amiodarone induced iodine load.

Declarations

Statements & Declarations
Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Acknowledgement

The article is dedicated to the memory of Professor Ivo Baschieri (+2014), who originally focused the problem and inspired this research.

Contributions

All authors contributed to the study conception and design, read and approved the final manuscript. Material preparation and data collection and analysis were performed by Giulia M., G.P. and L.F. The first draft of the manuscript was written by Giulia M.

Consent to publish

The participants have consented to the submission of the manuscript to the journal.

Ethics approval

Authors’ local ethics committee approved the study.

References

21. M.F. Erdoğan, S. Güleç, E. Tutar, M. Güldal, N. Başkal, G. Erdoğan, HLA-B40-, HLA-Cw3-, and HLA-DR5-Associated Susceptibility to Amiodarone-Induced Thyroid Dysfunction. Thyroid 10(4), 369–370 (2000 Apr)


Figures
Figure 1

Box-plots showing the magnitude of urinary iodine excretion at 6 months and 1 year from amiodarone initiation stratified for thyroid disorder development.
Figure 2

Graphical representation of 24h-urinary iodine excretion levels after amiodarone withdrawal at 4 months, 6 months and 1 year stratified for thyroid disorder development.