Dronedarone and Amiodarone Induce Dyslipidemia and Thyroid Dysfunction in Rats

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Key Words
Dronedarone • Amiodarone • Thyroid dysfunction • Dyslipidemia

Abstract
Background/Aims: Amiodarone, a thyroid hormone-like molecule, can induce dyslipidemia and thyroid dysfunction. However, the effects of dronedarone on lipid metabolism and of both dronedarone and amiodarone on thyroid function and lipid metabolism remain unknown.

Methods: Fifty male Sprague-Dawley rats were randomly divided into 5 groups (10 in each group): normal control (NC), amiodarone-treated (AMT), dronedarone-treated (DRT), rats treated with amiodarone combined with polyene phosphatidylcholine (AC), and rats treated with dronedarone combined with polyene phosphatidylcholine (DC). Rats were given amiodarone (120 mg/kg/d), dronedarone (120 mg/kg/d), and polyene phosphatidylcholine (200 mg/kg/d) for 13 weeks. At the end of weeks 4, 8, 12, and 13, plasma-free triiodothyronine (FT3), free thyroxine (FT4), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c) were determined. At the end of this protocol, rats were sacrificed and the thyroid glands were isolated, weighed, and examined histopathologically. The protein expression of Bcl-2 was measured by immunochemical staining. The mRNA expression of thyroglobulin (Tg), type-1 deiodinase (D1), and thyroid peroxidase (TPO) were detected by polymerase chain reaction (PCR).

Results: Compared with the NC group, FT3 and FT4 levels in the DRT and DC groups significantly increased at week 4 but declined thereafter. The AMT and AC groups had lower FT3 levels but comparable FT4 levels. The levels of TG, LDL-c, and HDL-c in the NC group were lower than those in the other groups whereas the LDL-c/HDL-c ratio was lowest in the AMT group. Bcl-2 expression significantly increased in the DRT group. The mRNA expression of Tg increased whereas the mRNA expression of D1 decreased. Dronedarone induced hyperthyroidism at the early stage and hypothyroidism at the late stage whereas amiodarone only caused hypothyroidism.

Conclusion: Both dronedarone and amiodarone can induce dyslipidemia and increase the levels of TC, LDL-c, and HDL-c, and these effects may be associated with thyroid dysfunction.
Introduction

Although widely used in the clinic, amiodarone (AM) may induce hepatic injury, thyroid dysfunction, and pulmonary toxicity [1-3]. Theoretically, AM induces thyroid dysfunction by the mechanisms associated with high iodine intake, elevation of oxidative free radicals, autoimmunity, direct effects of the drug itself, or any combination of these mechanisms [4-6]. AM contains up to 50 to 100 times the recommended daily dose of iodine [1-3], which leads to changes in thyroid hormone (TH) synthesis, metabolic disorders, or the direct damage to follicular cells. Dronedarone (DR) is a noniodinated benzo furan derivative of AM developed for the treatment of atrial fibrillation and a potent blocker of multiple ion currents [4-11]. AM, because of its similarity to TH, may compete for TRβ1 receptor binding sites in hepatic cells, which can decrease LDL-c receptor levels at both mRNA and protein levels. TH can reverse AM-induced dyslipidemia [12, 13]. Disruption of LDL receptors, in turn, disturbs the respiratory electron transport chain and prevents the transformation of TG into very-low-density lipoprotein (VLDL) [12-15]. Other studies have shown that AM causes dyslipidemia, which is characterized by elevated TG, LDL-c, and HDL-c, promotes cholesterol accumulation and formation of cholesterol deposits, and inhibits lipid metabolism [12-20]. Moreover, AM suppresses the activity of microsomal triglyceride transfer protein (MTP), resulting in decreased secretion of hepatic lipoprotein and decreased blood levels of TG and Apo-B in a dose-dependent manner. It is not clear whether AM inhibits MTP activity directly or by adhering to the lipid surface [15]. Considering that the half-life of AM is approximately 13–30 days, we evaluated its activity for 13 weeks to determine the correlation between concentration, cumulative dosage, and adverse reactions. To the best of our knowledge, no previous reports have evaluated the effects of DR on lipid metabolism. Therefore, in this study, we explored the effects of AM and DR alone or in combination with polyene phosphatidylcholine (a hepatic protective agent) on thyroid function and lipid metabolism.

Materials and Methods

Animals

Fifty male Sprague-Dawley rats weighing 180 – 220 g were purchased from the Zhejiang Province Animal Center (Certification: SCXK (Zhejiang) 2008–2008). After animal rearing for one week, the rats were randomly divided into 5 groups (10 in each group): normal control (NC), AM-treated (AMT), DR-treated (DRT), rats treated with AM combined with polyene phosphatidylcholine (AC), and rats treated with DR combined with polyene phosphatidylcholine (DC). Rats were given AM (120 mg/kg/d), DR (120 mg/kg/d), and polyene phosphatidylcholine (200 mg/kg/d) for 13 weeks. The doses of AM and polyene phosphatidylcholine were selected on the basis of the equivalent dose conversion coefficients between human and animal body surface area and our preliminary laboratory tests. Rats were monitored each morning for movement, breathing rate, fur condition, and signs of normal defecation.

The animals were sedated with ketamine (at a dose of 10 mg/100 g) and anesthetized with 7% choral hydrate (at a dose of 1 ml/100 g). Subsequently, the liver and thyroid glands were removed and weighed at the end of week 13. Organ coefficient (organ weight/body weight) was calculated as percentage. The study was approved by the Ethical Committee of the Second Hospital of Jiaxing. All experiments were conducted in accordance with the guidelines of the Institutional Animal Care Committee of Zhejiang Province Animal Center.

Reagents

AM tablets (certification No. 175) and DR-coated tablets were purchased from Sanofi-Aventis (certification code HK-59499). FT3, FT4, and TSH detection kits were purchased from Abbott Laboratories (NY, USA). Bcl-2 immunohistochemical ABC staining kit was purchased from Santa Cruz (CA, USA); Libor AEL200 electronic analytical balance was purchased from Shimadzu (Japan); biological microscope image collection and analysis system was purchased from Motic (XiaMen, China), FORMA Series II Water-Jacketed CO₂ incubator was purchased from Thermo Scientific (MA, USA); enzyme standard instrument (model 680 microplate reader) was purchased from Bio-Rad (CA, USA).
Plasma assay
Blood was collected from the caudal vein of fasted rats at the end of weeks 4, 8, and 12, and from the abdominal aorta at the end of week 13, after the animals were anesthetized with choral hydrate. Plasma cholesterol and triglyceride levels were determined using a fully enzymatic kinetic UV method (Cobas analyzer, Boehringer-Mannheim). Lipoprotein concentration (HDL-c, LDL-c) was also calculated. The measurement of the HDL-c levels depended on the cholesterol concentration in the supernatant after lipoprotein precipitation with heparin/MnCl₂. The sum of the HDL-c and LDL-c levels depended on the cholesterol concentration in the supernatant after lipoprotein precipitation with 10% SDS. Therefore, the LDL-c levels were calculated by subtracting the HDL-c levels from all HDL-c and LDL-c concentrations. Free triiodothyronine (FT3) and free thyroxine (FT4) were measured using an in-house radioimmunoassay (RIA).

RNA extraction and semi-quantitative RT-PCR
Thyroid glands were snap frozen in liquid nitrogen and stored at –80°C prior to RNA extraction. Total RNA was isolated using Trizol reagent (Qiagen, German) following the manufacturer’s instructions. RNA was diluted in RNase-free water and quantified using a NanoDrop ND-1000 spectrophotometer. The M-MLV enzyme (Qiagen, German) was used to produce cDNA by reverse transcription and the cDNA was stored at –20°C. One microgram of total cDNA was amplified from each sample by real-time PCR (RT-PCR). The following RT-PCR primers (Sangon Biotech, Shanghai, China) were used: beta-actin (GenBank EF:15276.1) forward 5’–CTT CCA GCC TTC CTT CCTGG–3’ , reverse 5’–CTT CCA GCC TTC CTT CCTGG–3’; Tg (GenBank AB679745.1) forward 5’–TGG CAA CCT CAT CGTAG–3’ , reverse 5’–GAT AAG CCC ATC GTCCT–3’; TPO (GenBank NM-019353.2) forward 5’–AGC TAT GGC AGT AAT GCTGG–3’ , reverse 5’–GCA GAC TGA AAC CAT CTTCG–3’.

To measure gene expression, 2.0 μL of cDNA was combined with 23.0 μL of the reaction mix (0.5 μL of forward primer, 0.5 μL of reverse primer, 0.2 μL of TaqMix (Qiagen, Germany), and 16.8 μL of distilled water). The thermocycler conditions were: 95°C for 5 min for initial denaturation, followed by 23 cycles at 95°C for 30 s, 60°C for 30 s, 72°C for 30 s for denaturation, annealing, and polymerization, respectively, followed by annealing at 72°C for 10 min for the amplification of beta-actin. The reaction conditions were slightly different for Tg: 25 cycles at 95°C for 30 s, 55°C for 45 s, and 72°C for 30 s. TPO was amplified with 27 cycles at 95°C for 30 s, 60°C for 30 s, and 72°C for 30 s. Samples were run on a 2% agarose gel for semi-quantitative analysis using StepOne Plus software (Life Technologies, CA, USA).

Immunohistochemistry analysis of Bcl-2
Thyroid tissue samples were fixed in formalin and embedded in paraffin, and section thickness was 4 μm. Endogenous peroxidase was inactivated with a methanol solution containing H₂O₂ (1:50) for 10 min and washed with PBS. The tissue sections were blocked with 1.5% serum for 30 min, incubated with anti-rat Bcl-2 primary antibody (1:100) overnight, followed by incubation with anti-rat Bcl-2 secondary antibody for 30 min and rinsing with PBS. Subsequently, samples were incubated with AB enzymes for 30 min and rinsed in PBS. Positive signals were detected using peroxidase chromogenic substrates. The negative control included PBS instead of the secondary antibody.

Histological analysis
For histopathological examination, thyroid and liver samples were fixed with 4% formaldehyde, trimmed, embedded in paraffin, sectioned, stained with hematoxylin and eosin (HE), and examined on a light microscope. Typical pathological changes were examined with transmission electron microscopy (TEM). Other thyroid samples were fixed in 1% osmic acid at 4°C, embedded in Epon 812, and cut in semi-thin and ultra-thin sections. These tissue sections were incubated in 0.5% uranyl acetate for 8 minutes, rinsed with water, stained with a drop of lead citrate, dried, and examined on an H-600A electron microscope.

Statistical analysis
The results were analyzed by SPSS version 16 and repeated-measures ANOVA was used. Least significant difference multiple comparisons were conducted to determine the homogeneity of variance between the groups. Dunnett’s test was used to determine the heterogeneity of variance for T3 after applying Welch’s correction. Row rank tests and analysis of variance tests were performed according to the
rank grouping using a non-normal distribution. Bivariate correlation tests were performed to evaluate FT3 and FT4 levels; a partial correlation test was applied after deducting the grouping factor. The results were represented as mean ± SD and \( p < 0.05 \) was considered statistically significant.

**Results**

**Amiodarone and dronedarone lead to weight loss and organomegaly**

The rats from the treated groups showed signs of hair loss, dilation, and diarrhea compared with normal rats. The treated rats also lost weight between weeks 1 and 3 but restored it after this period (Fig. 1). Thyroid weight in the AM and AC groups increased and was statistically different from that in the DRT and DC groups. Moreover, the weight coefficient increased in the AM and AC groups (Fig. 2).

**Amiodarone and dronedarone disrupt hepatic lipid homeostasis**

TC levels were significantly elevated in the AM and AC groups. In the DRT and DC groups, these levels were slightly higher than those in the NC group, except at week 12 (\( P < 0.05 \)). TG levels in the AC group were approximately 40%, 78%, 77%, and 78% greater than those in normal rats at weeks 4, 8, 12, and 13, respectively. AM treatment increased the TG levels. The changes in the HDL-c levels were similar to those in the TG levels. In addition, the HDL-c levels significantly increased in the AM and AC groups compared with the other three groups. The differences between the treated groups and the NC group were time-dependent from week 4 to 12 after treatment. The HDL-c levels in the AC group were approximately 40%, 103%, 98%, and 89% greater than those in normal rats at weeks 4, 8, 12, and 13, respectively. The LDL-c levels in the NC group were lower than those in the treated groups at all time points. The LDL-c levels decreased in the DC group and increased in the AC group.

To evaluate the relative changes in lipid levels, TG, TC, and LDL-c levels were normalized to HDL-c levels to predict the relative risk caused by dyslipidemia. The TC/HDL-c and TG/HDL-c ratios were higher in the NC group compared with the other groups whereas the AM and AC groups had the lowest TG/HDL-c ratio. The LDL-c/HDL-c ratio in the DRT and DC groups was higher than in normal rats (but not statistically significant) whereas the ratio in the AM and AC groups was lower than in the untreated group at all the time points, except at week 4 (Fig. 3).

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**Fig. 1.** Body weight in the study groups. * \( P < 0.05 \) versus control, ** \( P < 0.01 \) versus control.

**Fig. 2.** Amiodarone induced thyroid and hepatic organomegaly. Thyroid weight and weight coefficient significantly increased in the AMT group but significantly decreased in the DR-treated group (A, B). Compared with NC, * \( P < 0.05 \), \( P < 0.01 \); compared with AMT, \( P < 0.05 \), \( P < 0.05 \); compared with AC, \( P < 0.05 \), \( P < 0.05 \).
Fig. 3. Amiodarone and dronedarone induced dyslipidemia. AM and DR increased TC (A) and HDL-c levels (C). TG levels increased in the AMT group compared with the other groups (B). LDL-c levels increased in the AM- and DR-treated groups compared with the untreated group (D). TC/HDL-c and TG/HDL-c levels were higher in the NC group compared with the treated groups whereas TG/HDL-c levels were lower in the AMT and AC groups (E, F). The LDL-c/HDL-c ratio was higher in the DRT and DC groups than in the NC group but lower in the AMT and AC groups compared with the untreated group at all the time points, except at week 4 (G). Compared with NC, \( P < 0.05 \), \( P < 0.01 \); compared with AMT, \( P < 0.05 \), \( P < 0.01 \); compared with AC, \( P < 0.05 \), \( P < 0.01 \); compared with DRT, \( P < 0.05 \), \( P < 0.01 \). Compared with DC, \( P < 0.05 \), \( P < 0.01 \).

Table 1. Both amiodarone and dronedarone can induce thyroid dysfunction. Denote: Compared with NC, \( P < 0.05 \), \( P < 0.01 \); compared with AMT, \( P < 0.05 \), \( P < 0.05 \); compared with AC, \( P < 0.05 \), \( P < 0.05 \); compared with DRT, \( P < 0.05 \), \( P < 0.05 \)

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Both amiodarone and dronedarone induce thyroid dysfunction

FT3 levels significantly increased in the DRT and DC groups but remained lower than those in the NC group, which was obvious at week 8. During the whole experiment, the FT3
Fig. 4. The correlation between FT3 or FT4 with serum lipids. The correlation between (A) FT3 or (B) FT4 with TC, TG, HDL-c and LDL-c levels was analyzed.
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levels in the AM and AC groups were lower than in normal rats. The FT4 levels were lower in normal rats only at week 4 (P < 0.05). After 4 weeks of treatment, the FT4 levels in the AM and AC groups were similar to those in the NC group; however, by the 12th week, these levels were slightly lower than those in the NC group (P < 0.05). In addition, the FT4 levels significantly decreased in the DRT and DC groups compared with the other three groups (P < 0.05, Table 1).

Correlation between FT3, FT4, and serum lipids

The bivariate correlation analysis revealed that FT3 levels had a negative correlation with TC, HDL-c, and LDL-c levels but not with TG (Fig. 4A). The FT4 levels had a positive correlation with TC, TG, and HDL-c levels but not with the LDL-c levels (Fig. 4B). The partial tests, after deducting the grouping factors, yielded the same result.
Amiodarone and dronedarone damage the thyroid gland

The histopathological examination of the thyroid indicated the presence of damaged follicular epithelial cells with blurred follicular boundaries in the AM and AC groups and conspicuous thyroid matrix proliferation and cell damage in the DRT and DC groups (Fig. 5). TEM examination revealed that AM induced cavitation, mitochondrial cristae disappearance, formation of thyroid follicular cells, and endoplasmic reticulum expansion in the DRT group. Organelle disappearance, cavitation, and structure blunting were observed in the DC group (Fig. 6).

Dronedarone increases Bcl-2 expression in the thyroid gland

The immunochemistry results indicated a significant increase in the Bcl-2 expression in the thyroid gland in the DRT group and a slight increase in expression in the DC group compared with the negative and normal controls. However, no significant differences were observed between the AMT, AC, normal, and negative control groups (Fig. 7).
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RT-PCR

Compared with the controls, the mRNA expression of Tg and TPO significantly increased whereas D1 level increased slightly in the AMT group. DR had no influence on the mRNA expression of Tg and D1. The expression of TPO and D1 was significantly lower in the AC and DC groups (Fig. 8).

Discussion

Our study showed that DR induced hyperthyroidism at an early stage but eventually caused hypothyroidism at the end of the experimental period (13 weeks). By contrast, AM caused hypothyroidism throughout the experimental period. In addition, we found that both drugs could lead to dyslipidemia, which was possibly related to thyroid dysfunction induced by the repeated administration of these drugs over time.

AM has been widely used in clinical applications, although it has been broadly recognized that it induces thyroid dysfunction by the mechanisms of high iodine intake, accumulation of oxidative free radicals, autoimmune effects, direct effects of the drug, or a combination of these mechanisms; in addition, its use will often lead to metabolic disorders of thyroid hormone synthesis and direct damage to follicular cells [2-5]. AM inhibits peripheral (D1), resulting in increased T4 and T3 levels and decreased T3 levels. The inhibition of the transformation of T4 into T3 reduces the amount of T3 receptors in the pituitary glands, causing a decline in TSH levels [6-11]. However, contrary to these findings, some studies have shown that AM and its metabolite, desethylamiodarone (DEA), can reduce type 2 deiodinase activity in a noncompetitive manner and weaken T4 feedback mechanisms, leading to increased TSH levels [10]. AM and particularly DEA can exhibit toxicity towards thyroid follicular cells and induce thyroid changes, apoptosis, necrosis, inclusions, and endoplasmic reticulum osteoporosis. AM, when combined with phospholipids, can form multilayer inclusions, which are strong inducers of cell damage [5, 6]. In the present study, both AM and DR treatments induced thyroid dysfunction at an early stage, causing significant damage in as little as two months of use. The DR-treated groups exhibited hyperthyroidism by the 4th week and hypothyroidism after this period. In addition, thyroid Bcl-2 mRNA expression increased compared with the normal control and negative control groups, and
A similar result was observed in tissue samples on TEM examination. Our findings indicate that DR directly damages thyroid follicular cells, resulting in the increased release of FT3 and FT4 and induction of hyperthyroidism at an early stage. As the follicular cells lose their secretory capacity, thyroid hormone synthesis declines, leading to hypothyroidism after the initial effect of increased thyroid activity at an early stage. The AM-treated groups exhibited hypothyroidism throughout the study period, and it was more pronounced than the hypothyroidism induced by DR. The inhibition of deiodinase resulted in a compensatory decline in the FT3 levels whereas the FT4 levels increased. After the initial stage, FT4 levels decreased, indicating that AM not only caused hypothyroidism but also inhibited deiodinase. Our results were consistent with those from previous studies, which indicated that iodine was not the sole cause of AM-induced thyroid dysfunction.

To the best of our knowledge, this is the first study to examine the dynamic effects of DR on lipid metabolism and reveal that both DR and AM induce dyslipidemia. Considering the absence of changes in HDL-c in the short term, we monitored the animals for 13 weeks and found that the treated groups showed a significant increase in TC, LDL-c, and HDL-c. By promoting cholesterol accumulation and inhibiting lipid metabolism, AM can decrease the abundance of LDL receptors in hepatic cells at both mRNA and protein levels [12-14]. The decreased LDL receptor levels disturb the respiratory electron transport chain, prevent the transformation of TG to VLDL, and inhibit both PPARα activity and β-oxidation [15]; this results in changes in the mitochondrial membrane potential due to the accumulation of TG and lipid droplets in hepatic cells, and this accumulation may lead to non-alcoholic fatty liver disease [12-21]. AM also impairs hepatic lipoprotein secretion, thereby decreasing blood TG and Apo-B levels in a dose-dependent manner. It is not clear whether AM directly inhibits MTP activity or does so through mechanisms of lipid adherence to the surface [15]. The increase in the levels of TC, TG, and LDL-c increase the risk of cardiovascular disease [18]. Therefore, we normalized these levels to HDL-c levels using the LDL-c/HDL-c, TG/HDL-c, and TC/HDL-c ratios to evaluate the relative risk of cardiovascular disease. Interestingly, the LDL-c/HDL-c and TG/HDL-c ratios decreased in the AM-treated groups compared with the normal control group but increased in the DR-treated groups. The difference in these results may be explained by the observation that the absolute range of HDL-c increases more than the LDL-c range in the AM-treated group whereas DR follows the opposite trend. Correlation tests show that dyslipidemia may be related to thyroid dysfunction. Hudig et al. have proposed that AM, being similar in structure to thyroid hormone, may compete for TRβ1 receptor binding sites in hepatic cells and consequently decrease the LDL-c receptor levels at both mRNA and protein levels [20]. Although other studies have suggested that DR and its metabolite DEA selectively bind to TRα1, but not to TRβ1, they do not indicate what other mechanisms may be involved in DR-induced dyslipidemia [10]. Therefore, we sought to better elucidate the mechanisms by which DR induces dyslipidemia.

The less side effect of DR on thyroid was widely accepted and confirmed in clinic use. However, our results indicate that DR may be not as safe as it was reported, suggesting that the thyroid dysfunction of DR may be related to the dose of DR. For the future study about the side effect of DR, a dose-ranging study should be employed. Besides, since our data are all from rats, relevant clinical data needs to be collected to analyze the effect of DR on lipid metabolism in human.

AM is classified as a class III antiarrhythmic agent for acting primarily by prolonging the cardiac action potential duration through blocking cardiac potassium channels without change the expression of transient receptor potential cation channel family members [22]. But it also has been exhibited the effects of blocking sodium and calcium channels [23]. Lipids, especially the cholesterol plays an important role in cellular ion homeostasis [24]. So the relationship between AM or DR caused disturbed lipid metabolism and ion channels blocking should be another direction to understand the transient and prolonged effect of AM or DR.
Conclusions

Herein we have demonstrated that both DR and AM can induce dyslipidemia and increase the levels of TC, LDL-c, and HDL-c, and these effects may be associated with thyroid dysfunction. DR induces hyperthyroidism at an early stage but causes hypothyroidism at a late stage whereas AM primarily causes hypothyroidism; however, the underlying mechanisms need to be further investigated.

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Disclosure Statement

The authors declare that they have no competing interests.

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