Chronic Amiodarone Evokes No Torsade de Pointes Arrhythmias Despite QT Lengthening in an Animal Model of Acquired Long-QT Syndrome

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Background—Amiodarone is an effective antiarrhythmic drug rarely associated with torsade de pointes arrhythmias (TdP). The noniodinated compound dronedarone could resemble amiodarone and be devoid of the adverse effects. In the dog with chronic complete atrioventricular (AV) block (CAVB) and acquired long-QT syndrome, the electrophysiological and proarrhythmic properties of the drugs were compared after 4 weeks of oral treatment.

Methods and Results—Amiodarone (n = 7, 40 mg · kg⁻¹ · d⁻¹) and dronedarone (n = 8, 20 mg/kg BID) were started at 6 weeks of CAVB (baseline). Six dogs served as controls. Surface ECGs and endocardially placed monophasic action potential catheters in the left (LV) and right (RV) ventricles were recorded to assess QTc time, action potential duration (APD), interventricular dispersion (ΔAPD = LV APD minus RV APD), early afterdepolarizations (EADs), ectopic beats, and TdP. Both amiodarone (+21%) and dronedarone (+31%) increased QTc time. Amiodarone showed no increase in ΔAPD in 4 of 7 dogs, whereas dronedarone augmented ΔAPD in 7 of 8 animals. After dronedarone, TdP occurred in 4 of 8 dogs with the highest ΔAPD (105 ± 20 ms). TdP was never seen with amiodarone, not even in the dogs that had ΔAPD values comparable to those with dronedarone. Furthermore, a difference existed in EADs and ectopic activity incidence (dronedarone 3 of 8; amiodarone 0 of 7), which was also seen during an epinephrine challenge.

Conclusions—In the CAVB dog model, both amiodarone and dronedarone prolong QT time (class III effect). The absence of TdP with amiodarone seems to be related to homogeneous APD lengthening in the majority of dogs and the lack of EADs and/or ventricular ectopic beats in all. (Circulation. 2001;104:2722-2727.)

Key Words: antiarrhythmia agents • electrophysiology • hypertrophy • action potentials

Amiodarone is the most potent antiarrhythmic drug in the prevention of life-threatening ventricular arrhythmias and demonstrates a very low incidence of torsade de pointes arrhythmias (TdP).¹⁻⁴ The noncardiac adverse effects of amiodarone, however, attributed to the iodinated nature of the molecule, limit its clinical applicability.⁵,⁶ The noniodinated benzofuran derivative dronedarone, which is structurally related to amiodarone, could possess similar antiarrhythmic efficacy as well as the low proarrhythmic potential of amiodarone and be devoid of the unwanted side effects.⁷⁻⁹

The anesthetized dog with chronic complete atrioventricular (AV) block (CAVB) and acquired long-QT syndrome is a suitable model to assess the proarrhythmic potential of intravenously administered antiarrhythmic drugs and to study factors involved in acquired TdP.¹⁰⁻¹⁵ TdP in this model depends on (1) bradycardia, (2) long repolarization times, (3) large regional dispersion of repolarization, and/or (4) afterdepolarizations and triggered ectopic activity.¹⁰,¹⁵ The aim of the present study was to determine and compare the electrophysiological changes and possible proarrhythmic consequences of chronic oral administration of amiodarone and dronedarone in this animal model.

Methods

General

Twenty-seven mongrel dogs (weight 26 ± 5 kg, 18 female) were subjected to an initial experiment for creation of CAVB and implantation of an epicardial pacing electrode. The procedure, anesthesia, ventilation, and preoperative and postoperative care have been described in previous articles from our group.¹⁰,¹¹,¹⁵ The actual study started at 6 weeks of CAVB, because the heart had then reached a stable state in the different ventricular remodeling processes.¹⁴

Animal handling was in accordance with the European Directive for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (European Union Directive No. 86/609/CEE).
Studied in Anesthetized Dogs at 6 and 10 Weeks of CAVB

Figure 1 provides a flow chart of the experiment performed at 6 and 10 weeks of CAVB, consisting of electrophysiological and hemodynamic recordings at baseline and during proarhythmic challenges.

A 6-lead surface ECG, 2 endocardial monophasic action potentials (MAPs, EP Technologies Inc) in the left (LV) and right (RV) ventricles, and an LV pressure signal (Sentron Europe Inc) were simultaneously registered and stored. For definitions, amplifications, and filter settings, we refer to previous publications.10,11,15

Two intervention protocols were performed to evoke arrhythmias: (1) short-long-short pacing from the RV MAP (4·600 ms + 1200 ms + extrastimulus) and (2) IV administration of epinephrine (1 μg · kg⁻¹ · min⁻¹ for 20 minutes (Figure 1). Six dogs were excluded from the study before the start of amiodarone or dronedarone because of clinical signs of heart failure in 1 animal and inducible TdP by pacing in 5 animals. The latter is associated with sudden cardiac death in this model, disallowing screening for proarrhythmic activity in 5 consecutive ectopic beats, or (4) monomorphic nonsustained ventricular tachycardia (MVT, >5 consecutive ectopic beats), or (4) TdP.

Determination of Drug Levels

Venous blood samples were taken weekly. Myocardial tissue samples (~1 cm³) were obtained from the free wall of both ventricles at death. Analyses of drug plasma and tissue levels, including metabolites (n-monodebutyldronedarone and n-desethylamiodarone) were performed by the Department of Pharmacokinetics, Sanofi-Synthélabo, Montpellier, France. For details concerning analyses, see Reference 9.

Statistics

Pooled data are expressed as mean±SEM except for the arrhythmia scoring data during epinephrine administration, which are expressed as mean±SEM. Serial comparisons were performed by paired Student’s t test and single parameters between independent groups by 2-way ANOVA with a post hoc Bonferroni t test. Statistical analysis of the time-dependency studies was done by ANOVA for

Studies in Conscious Dogs Between 6 and 10 Weeks of CAVB

Both during idioventricular rhythm (IVR) and at a paced cycle length (CL) of 1000 ms (pacing from the LV epicardial electrode), the QT time and ventricular effective refractory period (VERP) were assessed every week. VERP was determined at twice diastolic threshold by delivering an extrastimulus at incremental steps of 5 ms.

Data Analysis and Definitions

Figure 1 shows the time periods of the electrophysiological and functional measurements and arrhythmia scoring.

The following parameters were measured offline: LV end-systolic pressure, LV end-diastolic pressure, LV peak rate of pressure rise (+dP/dt₉₀), CL-IVR, QT time, and duration of the LV and RV MAP (MAPD) at 100% repolarization. QTc time was calculated by the Van de Water formula. Furthermore, the planimetric area of the JT wave (J₉₀, mV · ms) in lead II of the surface ECG was assessed as a noninvasive parameter of dispersion of repolarization.

All data presented are the mean of 5 consecutive beats during stable CL-IVR after ≥1 hour of anesthesia. Interventricular dispersion (ΔMAPD) was calculated as LV MAPD minus RV MAPD. Early afterdepolarizations (EADs) were assessed on the MAP signals. Spontaneously occurring ventricular ectopic beats were counted (1) before catheter introduction during a 5-minute time interval and (2) during the last 5 minutes of the 20-minute epinephrine infusion period. An ectopic beat was defined as a ventricular complex having a coupling interval of <50% CL-IVR. Arrhythmic activity was scored on the basis of (1) single ectopic beats, (2) consecutive ectopic beats, (3) monomorphic nonsustained ventricular tachycardia (MVT, >5 consecutive ectopic beats), or (4) TdP.
Electrophysiological and Hemodynamic Results Before and After 4 Weeks of Amiodarone or Dronedarone Treatment Compared With the Control Group

<table>
<thead>
<tr>
<th></th>
<th>Control 6 Weeks CAVB</th>
<th>Before Amiodarone (n=7)</th>
<th>Before Dronedarone (n=8)</th>
<th>Control 10 Weeks CAVB (n=6)</th>
<th>Amiodarone (n=7)</th>
<th>Dronedarone (n=8)</th>
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<tr>
<td>CL-IVR, ms</td>
<td>1145±115</td>
<td>1110±140</td>
<td>1210±160</td>
<td>1215±75</td>
<td>1805±360†</td>
<td>1630±475</td>
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<td>QRS time, ms</td>
<td>76±11</td>
<td>82±9</td>
<td>85±9</td>
<td>73±13</td>
<td>89±9</td>
<td>94±15†</td>
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<td>QT time, ms</td>
<td>360±55</td>
<td>340±40</td>
<td>370±50</td>
<td>380±50</td>
<td>470±75†</td>
<td>515±40†</td>
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<td>QTc time, ms</td>
<td>345±40</td>
<td>330±35</td>
<td>350±50</td>
<td>360±45</td>
<td>400±60</td>
<td>460±30†</td>
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<td>JT area, mV · ms</td>
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<td>145±50</td>
<td>157±89</td>
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<td>LV MAPD, ms</td>
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<td>300±40</td>
<td>360±45†</td>
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<td>ΔMAPD, ms</td>
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<td>50±30</td>
<td>75±35</td>
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<td>LV ESP, mm Hg</td>
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<td>120±15</td>
<td>115±14</td>
<td>100±12</td>
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<td>100±14</td>
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<td>LV EDP, mm Hg</td>
<td>12±5</td>
<td>5±4*</td>
<td>15±7</td>
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<td>LV +dP/dtmax, mm Hg/s</td>
<td>2740±115</td>
<td>3205±990</td>
<td>2790±620</td>
<td>1940±400</td>
<td>2250±610</td>
<td>2035±225</td>
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</table>

ESP indicates end-systolic pressure; EDP, end-diastolic pressure.
*P<0.05 amiodarone vs dronedarone; †P<0.05 vs control, ANOVA.

Repeated measures. Incidence was compared by χ² testing. Values of P<0.05 were considered significant.

Results

Electrophysiological Studies in Conscious Dogs Between 6 and 10 Weeks of CAVB
All 21 animals survived the 4 weeks of drug administration. In 1 dog of the amiodarone-treated and 2 dogs of the dronedarone-treated groups, the VERP determinations could not be completed because of electrode dysfunction.

In the control group, the CL-IVR and QT times remained similar (CL-IVR 1245±150 ms and QT time 315±15 ms at 6 weeks CAVB versus 1270±185 and 320±25 ms at 10 weeks CAVB).

Both amiodarone (1230±185 to 1675±435 ms) and dronedarone (1145±165 to 1360±190 ms) had a significant bradycardic effect. QT time prolonged significantly for both drugs at IVR (amiodarone 290±15 to 355±26 ms and dronedarone from 295±25 to 365±30 ms). Also at 1000-ms paced CL, QT time (amiodarone +12% and dronedarone +13%) as well as VERP (amiodarone 191±13 to 223±18 ms and dronedarone 204±30 to 243±33 ms) increased (Figure 2).

Arrhythmias With Amiodarone and Dronedarone
At 10 weeks of CAVB, none of the animals in the control or amiodarone group showed EADs or spontaneous ectopic activity in the 5-minute period before catheter introduction. In contrast, 6 of 8 dronedarone animals showed EADs (P<0.01 versus amiodarone) on the LV MAP, of which 3 also developed considerable ventricular ectopic activity.

Studies in Anesthetized Dogs at 6 and 10 Weeks of CAVB
The baseline electrophysiological values were comparable between the 3 groups (Table, left). EADs, ectopic activity, and TdPs were absent. The hemodynamic parameters were also similar, although the amiodarone group had a relatively low LV end-diastolic pressure value. These electrophysiological and hemodynamic data are in agreement with data published previously in the CAVB dog.

Epinephrine administration decreased CL-IVR and all repolarization parameters, including ΔMAPD (data not shown). The average number of epinephrine-evoked ectopic beats and MVTs at 6 weeks of CAVB is depicted in Figure 3 (n=21, control 6 weeks).

The right side of the Table presents the electrophysiological and hemodynamic results after 4 weeks of treatment. The QT time and LV and RV MAPD were longer for both drugs compared with the control group. Dronedarone had a stronger “class III effect” eg, dronedarone increased QTc time from 350±50 to 460±30 ms (31%), whereas amiodarone increased QTc time from 330±35 to 400±60 ms (21%, P<0.05 for both). Remarkably, for the amiodarone group, the prolonged QT time was accompanied by an augmented ΔMAPD in only 3 dogs (Figure 4). As a consequence, ΔMAPD did not increase significantly (Table). In contrast, dronedarone affected LV MAPD far more than RV MAPD in 7 of 8 dogs, augmenting ΔMAPD significantly (Figure 4). Also, JT area increased in the dronedarone group (from 157±89 to 200±104 mV · ms), whereas the control and the amiodarone-treated groups remained similar (Table).

![Figure 3. Arrhythmia scoring for 5-minute period during epinephrine infusion for 2 control (6 and 10 weeks CAVB), amiodarone-, and dronedarone-treated groups. x axis, division between single ectopic beats (EB), consecutive ectopic beats (CEB), MVT, and Tdp; y axis, mean number of different arrhythmias per dog. Dronedarone group demonstrated significantly (*P<0.05) more ectopic activity.](http://circ.ahajournals.org/doi/10.1161/01.CIR.110.05.2724)
In the control group, spontaneous TdP was never seen, but it could be induced by pacing in 1 of 6 animals. In the amiodarone group, no spontaneous or pacing-induced TdP occurred. Multiple episodes of spontaneous TdP (Figure 5) were seen in 3 dogs with dronedarone treatment. Furthermore, TdP was inducible by pacing in 1 animal, in which EADs but no ectopic beats were observed, resulting in a total TdP incidence of 4 of 8 dronedarone-treated dogs. Subgroup analysis looking at LV MAPD resulted in an absence of ectopic beats and spontaneous or inducible TdP for those dogs having an LV MAPD <500 ms.

In the dronedarone-treated group only, epinephrine administration resulted in an increased number of ectopic beats (Figure 3).

Myocardial Tissue and Plasma Concentrations
The plasma levels of dronedarone (1.3±0.3 mg/L), amiodarone (3.5±0.6 mg/L), and their metabolites were in agreement with data published recently.9 The myocardial tissue data of amiodarone (LV 17.9±3.8, RV 13.3±3.8 mg/kg), n-desethylamiodarone (LV 12.7±2.9, RV 8.0±2.3 mg/kg), dronedarone (LV 13.5±3.8, RV 13.2±3.9 mg/kg), and n-monodebutyldronedarone (LV 2.8±0.7, RV 3.4±0.9 mg/kg) were comparable to data published by Latini et al.19 and Merot et al.20 The 3 animals showing an increased MAPD on amiodarone also tended to have higher tissue levels of the compound (LV 25.7±11.6 versus 12.0±2.6 mg/kg) and its metabolite (LV 16.7±10.6 versus 9.8±3.4 mg/kg) compared with the other 4 animals.

Autopsy Data
At autopsy, the heart weight/BW (12.4±1.2 g/kg in the control, 13.0±0.9 g/kg in the dronedarone, and 11.6±2.1 g/kg in the amiodarone groups), liver weight/BW (26.7±3.2, 28.1±4.4, and 30.4±2.3 g/kg, respectively), and lung weight/BW (12.6±2.9, 14.5±4.3, and 10.8±2.4 g/kg) ratios were similar in the 3 groups.

Discussion
In the CAVB dog, both amiodarone and dronedarone prolonged QT time and VERP significantly (Figure 2). These increases in QT time and VERP for amiodarone under conscious conditions are comparable to human data.21 Amiodarone, unlike dronedarone, evoked no EADs, ectopic beats, or TdP and did not increase dispersion of repolarization significantly. In contrast, other antiarrhythmic drugs administered intravenously in the CAVB dog, like dofetilide or almokalant, augmented dispersion of repolarization and elicited EADs, ectopic beats, and TdPs.10,15

Amiodarone does not fit well into conventional antiarrhythmic classification schemes. Used long-term, amiodarone

Figure 4. Individual data of QT time (left) and interventricular dispersion (ΔMAPD, right) are shown before (b) and after amiodarone (amio) or dronedarone (dron) treatment. Left, Amiodarone prolonged QT time in 6 of 7 dogs, but was associated with increase in ΔMAPD (right) in only 3 of 7 (●, left). Dronedarone increased QT time in all and ΔMAPD in 7 of 8 dogs (●), being associated with TdP for those dogs having highest ΔMAPD (●, right).

Figure 5. Spontaneously occurring TdP during chronic dronedarone treatment in an anesthetized CAVB dog. Four panels with lead II of surface ECG at 10 mm/s demonstrate several episodes of TdP during 17-minute period. Bottom, Single LV and RV MAPs are shown to exemplify ΔMAPD (520 minus 430 ms).
prolongs the ventricular APD and therefore is classified generally as a class III agent. However, the drug also possesses class I (sodium channel blockade), class II (anti-adrenergic), and class IV (calcium channel blockade) effects.5,8,22 The multiple ion channel interaction by amiodarone has been speculated to contribute to its minimal reverse use dependency and low incidence of clinical TdP arrhythmias, even in patients who develop TdP on other antiarrhythmics.5,22–24 Dronedarone, given either long-term or short-term, has been suggested to possess a similar electrophysiological profile, but the effects of chronic dronedarone on specific cardiac ion channels are still unknown.7–9

Arrhythmic Parameters: Dispersion

TdP is generally thought to be dependent on 2 interrelated mechanisms: the trigger (ectopic beat) and the substrate (dispersion).10,25 The length of the LV MAP plays an important role in both, either by creating regional dispersion of repolarization between the ventricles or by generating EAD-dependent triggered arrhythmias.26 Furthermore, EADs will contribute to dispersion when their presence in the ventricles is not homogeneous. Second, when EADs give rise to ectopic beats, electrical heterogeneity will be further augmented (eg, ∆MAPD), a concept that has been referred to as modulated dispersion of repolarization.27–29

Dronedarone increased ∆MAPD in 7 of 8 dogs (Figure 4), based on a more pronounced lengthening of the MAPD in the LV versus the RV. Despite QT lengthening and bradycardia, amiodarone prolonged the ventricular APDs homogeneously in 4 of 7 dogs, resulting in a nonsignificant overall increase of ∆MAPD. Similar results on equal or reduced transmural dispersion in 4 of 7 dogs, not even in those with a similar magnitude of ∆MAPD.

Therefore, the lack of TdP with amiodarone appears to be linked to the prevention of EADs and/or ectopic activity, even during proarrhythmic challenges with pacing protocols and epinephrine administration. Absence of EADs after amiodarone treatment was observed earlier in M cells17 and in isolated rabbit right ventricular tissue.31

Why dronedarone-treated animals respond differently is unclear, but this could be related to (1) unfortunate randomization, (2) the selected dosage, or (3) dissimilar electrophysiological effects. With respect to point 1, the 3 dogs showing TdP after dronedarone had relatively high LV MAPD at baseline (6 weeks CAVB) (mean 405 ± 25 ms) compared with amiodarone (310 ± 25 ms). The length of LV MAPD at baseline was recently described as a predisposing factor for (drug-induced) arrhythmias.16 Point 2, although the selected dosages showed similar increases in QT time under conscious conditions, differences in repolarization parameters were seen under anesthesia, which could have proarhythmic consequences. Indeed, subgroup analysis confirmed that LV MAPD values >500 ms in the dronedarone group were consistently associated with ectopic beats and TdP. Point 3, the different electrophysiological and arrhythmic outcomes of the drugs in the present study could suggest that chronic amiodarone exerts its beneficial effect by (1) modulating the ion channels differently, (2) inhibiting thyroid hormone activation in cardiac muscle, or (3) a combination of the two.5,22

Clinical Implications

The CHF-STAT, CAMIAT, and EMIAT trials showed that amiodarone lacked proarrhythmia and reduced the incidence of arrhythmias and arrhythmic death in high-risk patients.1,3,4 The present study demonstrates that the preventive effect of amiodarone on EAD formation and/or ventricular ectopic activity could account for the clinical safety and efficacy of the drug. The possible proarhythmic effects of dronedarone should be carefully evaluated in future clinical trials.

Limitations

The selection of only 1 dosage in relatively small groups and possible predisposing factors prevent us from drawing definite conclusions about the proarhythmic outcome of dronedarone.

Conclusions

Amiodarone is the first drug having pronounced class III effects, which do not result in TdP in this model. This is in agreement with the clinical safety of the drug and supports the validity of the model for screening arrhythmic potential of (anti-arrhythmic) drugs. The absence of TdP with amiodarone can be explained by (1) the absence of EADs and/or ventricular ectopic activity in all animals and (2) a homogeneous increase in LV and RV MAPD in the majority of dogs.

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