

## **RELATIONSHIP AMONG AMIODARONE, NEW CLASS III ANTIARRHYTHMICS, MISCELLANEOUS AGENTS AND ACQUIRED LONG QT SYNDROME**

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## Introduction

Acquired QT/QTc prolongation is essentially caused by drugs. The list of drugs involved is continuously increasing: antiarrhythmics Class I and III, antihistamines, psychotropics, anti-infectious, (antibiotics, antiretrovirus, fluconazole,) methadone, (frequently associated with HIV therapy to treat patients with opiate addiction) are the main categories involved. It is principally linked to a block of the outward potassium current  $I_{Kr}$ , with as a consequence a prolongation of the repolarization causing early after potentials and re-entry. Some drugs prolong QTc in a dose-dependent manner; others do so at any dose (1).

The term "repolarization reserve" expresses the variable risk of arrhythmia among individuals under the same drug blocking  $I_{Kr}$ . The hERG (human ether-à-go-go-related gene) potassium channel has elicited intense scientific interest due to its counter-intuitive kinetics and its association with arrhythmia and sudden death (SD). hERG blockade is involved in both antiarrhythmic pharmacotherapy and the pathogenesis of familial and acquired long QT syndrome (aLQTS). This reserve can be altered under various pathologic or genetic conditions. Pathophysiologically significant ion-channel mutations have been detected in only a minority of cases of aLQTS. Previously unsuspected LQTS mutations may be present in patients with antiarrhythmic drug-associated TdPs. A normal QTc interval does not exclude the risk of proarrhythmia (2). They are due to a perturbation of ventricular repolarization causing QT prolongation on surface ECG. aLQTS are caused mainly by drugs. In addition, can play a role as well as the metabolic processing of pharmacological agents by Cytochrome P450 and various inhibitors or inductors of this system which can influence the half life of drugs. Risk prediction is difficult particularly for non cardiovascular drugs and a low risk incidence. Another risk is to exclude patients from the benefit of an efficient drug for a serious but not frequent risk, at last an industrial risk for the manufacturer when a drug is withdrawn lately when important quantities of money have already been invested for its development.

Others causes of aLQTS are electrolytic disorders, cardiac disease (myocardial infarction, dilated cardiomyopathy, mitral valve prolapse, neurological diseases,

dietary deficiencies, severe malnutrition among anorexic patients, chronic arsenic exposure(3), cesium chloride supplement(4), female gender etc.

The diagnosis of TdP is easy on standard ECG although QT measurement and its heart rate variation remain uneasy.

The treatment of TdP immediate defibrillation for hemodynamic instability is based on heart rate acceleration by Isoprenaline or Cardiac pacing, potassium (if hypokalemic) and intravenous magnesium sulfate(5).

Other alternative or non drug therapy is removing causative agents.

Moderate hERG blockade may produce a beneficial class III antiarrhythmic effect. In contrast, a reduction in hERG currents due to either genetic defects or adverse drug effects can lead to hereditary or aLQTS characterized by action potential (AP) prolongation, lengthening of the QT interval on the surface ECG, and an increased risk for "torsade de pointes" arrhythmias and SD. Drug-induced LQTS is characterized by a prolonged corrected QT interval (QTc) and increased risk of a polymorphic ventricular tachycardia(PVT) known as torsade de pointes (TdP). Class III drugs prolong repolarization (increase refractoriness) by blocking outward potassium conductance (prolong QT interval), with typically little effect on the rate of depolarization (no effect on QRS interval).

All drugs that prolong QTc block the rapid component of the delayed rectifier current ( $I_{kr}$ ). Some drugs prolong QTc in a dose-dependent manner, others do so at any dose (1).The increasing understanding of hERG channel function and molecular mechanisms of hERG current regulation could improve prevention and treatment of hERG-associated cardiac repolarization disorders.

Most patients that develop drug-induced TdP have underlying risk factors. Female sex is the most common. Implicated drugs include class 1A and III antiarrhythmics, macrolide antibiotics, pentamidine, antimalarials, antipsychotics, arsenic trioxide, and methadone. These drugs should be used with caution in female patients prone to bradycardia.

### **Potassium Channel Blockade**

Potassium channels, particularly the channel giving rise to the "delayed rectifier current", are activated during the repolarization (Phase 3) of the AP. Blockade of

potassium channels prolongs AP duration (APd). Prolongation of APd usually results in an increase in effective refractory period. Many of the drugs that prolong repolarization (Class III drugs, potassium channel blockers) exhibit negative or reverse rate-dependence. These drugs have little effect on prolonging repolarization in rapidly depolarizing tissue. These drugs can cause prolongation of repolarization in slowly depolarizing tissue or following a long compensatory pause, leading to repolarization disturbances and TdP.

Repolarization of cardiomyocytes is mainly performed by the rapid component of the delayed rectifier potassium current,  $I(Kr)$ , which is encoded by the human ether-a-go-go-related gene (HERG). Inhibition of HERG potassium currents by class III antiarrhythmic drugs causes lengthening of the cardiac AP, which produces a beneficial antiarrhythmic effect. Conversely, excessive prolongation of the AP by a wide variety of antiarrhythmic and non-antiarrhythmic drugs may lead to aLQTS, which is associated with a risk for TdP arrhythmias and SD(6).

### **CLASS III ANTIARRHYTHMICS**

#### **I) MAIN REPRESENTATIVE AGENT**

- 1) Amiodarone.

#### **II) NEW GENERATION'S AGENTS**

- 2) Dofetilide
- 3) Dronedarone
- 4) Azimilide
- 5) Ibutilide.

#### **III) MISCELLANEOUS AGENTS**

- 6) Trecetilide
- 7) Tedisamil
- 8) Ersentilide
- 9) Ambasilide
- 10) Chromanol 293B
- 11) Sematilide

#### IV) OTHERS OLD AGENTS

12) Sotalol (combined class II/III)

13) Bretylium

Observation: In this manuscript we do not undertake the last one group IV

#### I) MAIN REPRESENTATIVE AGENT

##### 1) Amiodarone

Although amiodarone is approved by the US Food and Drug Administration only for refractory ventricular arrhythmias, it is one of the most frequently prescribed antiarrhythmic medications in the United States. The drug is the gold standard in the prevention of recurrence of atrial fibrillation (AF). Atrial electrical remodeling changed the efficacy of the antiarrhythmic agents in a different way. Amiodarone is among the most effective with the additional advantage of having little proarrhythmic potential. The favorable efficacy profile of amiodarone during electrical remodeling, particularly the marked increase in amiodarone on atrial refractory periods prolongation in early electrical remodeling, may explain its superior clinical efficacy over existing antiarrhythmic drugs(7). Amiodarone has a low incidence of cardiac adverse events, including TdP. In elderly women long-term amiodarone treatment could result of combined block of the rapid ( $I(Kr)$ ) and slow( $I(Ks)$ ) delayed current outward potassium current ( $I(K)$ ) components, translated to the ECG in a (more than expected) prolonged QT interval, an augmented transmural dispersion of repolarization (TDR) and an interrupted T wave. The unequal regression of repolarization lengthening made possible to individualize  $I(K)$  current components in the inscription of the interrupted T wave, which argues against the U wave as a separate entity. Silent ion channel gene mutations or polymorphisms and downregulation of beta-adrenergic activation of  $I(Ks)$  may underlie the unusual repolarization behavior. The unequal regression over time of amiodarone induced repolarization lengthening could have clinical significance(8). Amiodarone should be used with close follow-up in patients who are likely to derive the most

benefit, namely those with AF and left ventricular(LV) dysfunction, those with acute sustained VT, those about to undergo cardiac surgery, and those with implantable cardioverter-defibrillators and symptomatic shocks(9). Although this drug is highly effective in treating many arrhythmias, its large number adverse effects limits its clinical use. Adverse effects are common (more than 75% of patients receiving drug) and increase after a year of treatment; some toxicities result in death. Half-life of 25-110 days can prolong toxicity.

### **Main extra-cardiac side effects**

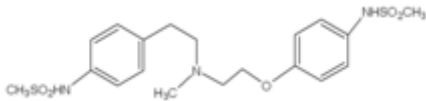
- 1) Pulmonary toxicity and fibrosis (10-15%, can cause death in 10% of those affected); can be irreversible. It is the most serious side-effect of amiodarone, and its detection and prevention are extremely important. Higher age and higher maintenance dose are risk factors (10). The short-term administration of amiodarone use post cardiac surgery does not seem to affect respiratory function(11);
- 2) Hyperglobulinemia: Seldom amiodarone therapy may be associated with hyperglobulinemia. Most of the patients with amiodarone-associated hyperglobulinemia have amiodarone-induced pneumonitis. Hyperglobulinemia may be a marker for a damaged organ, or it may have a pathogenetic role in the induction of pneumonitis(12);
- 3) Constipation in 20% of patients);
- 4) Hepatic dysfunction; can be irreversible;
- 5) Asymptomatic corneal deposits occur in all patients;
- 6) CNS effects (ataxia, dizziness, depression, nightmares, hallucinations);
- 7) Both hypothyroidism or hyperthyroidism (5% of patients) (13);
- 8) Cutaneous photosensitivity (25% of patients) and blue-grey discoloration of skin (less than 5% of patients);
- 9) Peripheral neuropathy;
- 10)Substantial increases in LDL-cholesterol concentrations often seen; phospholipidosis;

- 11) Enhances the effect of warfarin and increases the serum concentrations of digoxin, quinidine, procainamide, flecainide, theophylline and other drugs.

## II) NEW GENERATION'S AGENTS

### 2) DOFETILIDE (Tikosyn®)(Pfizer, Sandwich, Kent, UK)

**Structure:** Dofetilide is a novel, highly specific class III methanesulfonanilide anti-arrhythmic drug. The chemical name for dofetilide is N-[4-(2-{2-[4-(methanesulphonamido) phenoxy]-N methylethylamino}ethyl)phenyl]-methanesulphonamide.



#### Dofetilide

**Action Mechanism:** Dofetilide is a relatively new class III antiarrhythmic agent that selectively blocks the rapid component of the cardiac ion channel delayed rectifier current.

Dofetilide's mechanism of action relies on potent blockade of the rapidly activating, HERG currents (I<sub>Kr</sub>) inwardly rectifying component of the delayed rectifier potassium current (I<sub>Kr</sub>). The drug appears to primarily block activated channels and has a much lower affinity for closed and inactivated channels(14). At nanomolar concentrations this agent prolongs both the atrial and ventricular effective refractory periods and APd. Dofetilide does not appear to interact with other cardiac ionic channels, and this explains its minimal effects upon conduction velocity, myocardial contractility and systemic haemodynamics. Unlike other antiarrhythmic agents, oral dofetilide did not increase mortality in patients with a recent MI or congestive HF, hence its importance as an alternative medication for the pharmacological conversion of AF and flutter, and maintenance of SR after conversion in patients at high risk of SD (15).

Dofetilide prolongs the QT interval with little effect on QT dispersion.

No effect on conduction parameters PA, AH, M HV, PR or QRS intervals, sinus cycle length or sinus node recovery.

**Bioavailability:** The rate at which a drug is absorbed by the body is from 75% to 100%.

**Elimination:** renal and hepatic (CYP3A4 family). In patients with Kidney disease Higher blood levels may occur, which may increase the chance of side effects. Liver disease (severe) Safety in this condition is unknown.

**Doses:** For *oral* dosage form (capsules): Adults—125 to 500 mcg two times a day.

**Clinical use:** Termination of supraventricular (prevention of recurrent AF A flutter) and VT.( increasing the electrical threshold for inducible VT/VF.). Dofetilide is approved by the U.S. Food and Drug Administration (FDA) for conversion to and maintenance of SR in patients with persistent AF.

Dofetilide is not indicated in patients with paroxysmal AF.

## **MAIN TRIALS WITH DOFETILIDE**

**EMERALD trial:** (The European and Australian Multicenter Evaluative Research on AF Dofetilide) was a dose-finding study with the primary goal of assessing the safety and efficacy of oral dofetilide and sotalol in preventing recurrence of AF. In this study, 671 patients with AF were randomly assigned to receive dofetilide in dosages of 125 µg, 250 µg, or 500 µg twice/day, or sotalol 80 mg twice/day, or placebo. By day 3, 535 patients regained SR either pharmacologically (187 patients) or by electrical cardioversion (348 patients). The primary analysis compared the efficacy of dofetilide and placebo in maintaining SR. All dofetilide dosages were significantly more likely to maintain SR compared with placebo at 3, 6, and 12 months. Also, dofetilide administered as 500 µg twice/day was more effective than dofetilide 125 µg and sotalol. Three cases of TdP occurred, all in women receiving dofetilide 500 µg twice/day. This study suggests dofetilide is an effective new therapeutic option for AF. However, the relatively low dosage of sotalol and the fact that this study is published only in abstract form and precludes confirmation of only previously cardioverted patients included in the maintenance analysis creates questions regarding the validity of this trial. Oral magnesium l-lactate raises intracellular magnesium concentrations and lowers the QTc interval of patients receiving sotalol or dofetilide(16).



**SAFIRE-D trial:** In the Symptomatic Atrial Fibrillation Investigation Research on Dofetilide oral dofetilide was evaluated for its ability to convert and maintain SR in patients with chronic AF (85% of patients) or atrial flutter. This study was a double-blind, multicenter, placebo-controlled trial, with 325 patients enrolled. All patients aged 18-85 years with AF or atrial flutter of 2-26 weeks duration were eligible for enrollment. The study began with an in-hospital conversion phase of 3 days or 5 doses, followed by a 12-month maintenance phase. Patients whose SR could not be restored pharmacologically, underwent electrical cardioversion. Those patients whose rhythm did not convert either pharmacologically or electrically, were withdrawn from the study. Initially patients were randomly assigned to dofetilide 125, 250, or 500 µg twice/day or placebo. After the first 105 patients were enrolled, the dosing protocol was altered to adjust for baseline renal function (creatinine clearance) and change in QTc interval duration. In the maintenance phase, time to first relapse of AF or atrial flutter or completion of 12 months of follow-up was the primary end point measured for dofetilide versus placebo.

Of the patients entering the maintenance phase (250 patients), the probability of remaining in SR at 1 year was 40%, 37%, and 58% for the dofetilide 125-, 250-, and 500-µg groups, respectively, and 25% for placebo (500 µg vs placebo,  $p=0.001$ ). The median time to relapse of AF or atrial flutter in the placebo group was 27 days, whereas a dose-response relationship of 31, 179, and more than 365 days was observed for the dofetilide treatment groups. When evaluating the effects of baseline covariates on outcomes, it was found that patients with atrial flutter maintained SR better than did patients with AF ( $p=0.0004$ ). There were two cases of nonfatal TdP considered a result of dofetilide therapy; both occurred within the first 3 days of therapy. Prolongation of QTc duration accounted for 10 withdrawals, and one SD occurred. Dosage adjustment based on creatinine clearance or QTc prolongation was required in 33% of patients.

**The SAFIRE-D trial** found dofetilide to be significantly more effective in maintaining SR at 1 year, when compared with placebo. However, the absolute efficacy rates were moderate and probably the result of a high frequency of heart failure in the patient population (72% New York Heart Association [NYHA] class II or III). Finally, as a result of this trial, starting therapy in the hospital and

adjusting dosage based on creatinine clearance and QTc prolongation are required to minimize the risk of proarrhythmia.

**DIAMOND trial:** (Danish Investigations of Arrhythmias and Mortality on Dofetilide study) (17), dofetilide does not affect mortality in the treatment of patients post-MI with LV dysfunction. Because of the results of the DIAMOND study, many physicians use dofetilide in the suppression of AF in individuals with LV dysfunction.

**Side effects:** Due to its very specific mode of action, dofetilide has very few systemic side-effects. Dofetilide represents a novel and promising new class III agent (18).

Like other drugs that affect potassium currents, the prolonged QT interval occurring in the patients treated with dofetilide can be complicated by TdP. It is the most serious side effect. The incidence of TdP is dose-related, and is 0.3-10.5%. The risk appears to be dose-dependent, with an increased incidence of TdP associated with higher doses of dofetilide administered. The risk of inducing TdP can be decreased by taking precautions when initiating therapy, such as hospitalizing individuals for a minimum of three days for serial creatinine measurement, continuous telemetry monitoring and availability of cardiac resuscitation. Severity of HF, female gender, and QTc duration make it possible to identify patients with a high risk of early TdP when treated with dofetilide. Patients with recent MI less often had TdP compared with patients with chronic HF (19).

In patients with paroxysmal AF and normal LV function treatment with dofetilide was successful in less than 20% patients. Despite careful precautions, serious proarrhythmias, the major limiting side effect of dofetilide, still occurred during long-term follow-up(20). It is generally well tolerated but like other antiarrhythmic agents in its class, TdP may be induced as a consequence of therapy. This risk is minimized by dosage adjustment according to creatinine clearance and QT(c) interval, by selecting patients without known risk factors for TdP and by initiating treatment in a monitored hospital setting for the first 3 days.

*More common side effects are:* dizziness; fainting; fast or irregular heartbeat

*Less common:* Chest pain; confusion; facial or flaccid paralysis; numbness or tingling of the hands, feet or face; paralysis; pounding, slow heartbeat; slurred speech; swelling of the ankles, arms, face, feet, fingers, legs, lips, tongue, and/or throat; troubled breathing; unexplained shortness of breath; unusual tiredness or weakness; weight gain; yellow eyes or skin Abdominal or stomach pain; accidental injury; back pain; chills; cough; diarrhea; fever; flu-like symptoms; general feeling of discomfort or illness; headache; joint pain; loss of appetite; migraine; muscle aches and pains; nausea; rash; runny nose; shivering; sneezing; sore throat; sweating; trouble sleeping; vomiting.

**Pregnancy**—Dofetilide has not been studied in pregnant women. However, studies in animals have shown that dofetilide causes birth defects.

**Breast-feeding**— It is not known whether dofetilide passes into breast milk. However, the manufacturer does not recommend breast-feeding while taking dofetilide

#### **Interaction with others drugs**

- 1) Antiarrhythmic or other heart medicine, such as amiodarone (e.g., Cordarone) taken within the last 3 months or
- 2) Antibiotics like macrolides or trimethoprim, alone or in combination with sulfamethoxazole (e.g., Biaxin, E-Mycin, ERYC, Ery-Tab, Trimplex, Bactrim, Septra) (CYP3A4 family)
- 3) Ketoconazole (CYP3A4 family)
- 4) Bepridil
- 5) Cimetidine
- 6) Cisapride
- 7) Megestrol
- 8) Phenothiazines like prochlorperazine or trifluoperazine.
- 9) Tricyclic antidepressants like amitriptyline or desipramine.
- 10) Verapamil may cause irregular heartbeats.
- 11) Hydrochlorothiazide/Triamterene: may increase seric amount of dofetilide

### 3) Dronedarone

Dronedarone is an investigational antiarrhythmic benzofuran derivative agent that is designed to have similar cardiac effects to amiodarone but with fewer adverse effects(21). Dronedarone, is a potassium channel antagonist, chemically related to amiodarone. It is a new synthetic noniodinated derivative of amiodarone(22). It is being developed by sanofi-aventis as a class III antiarrhythmic agent for the treatment of AF and atrial flutter in the US and Europe. The drug has multiple electrophysiologic actions, similar to amiodarone, but without the iodine moiety seen with amiodarone. Dronedarone shares amiodarone's multichannel blocking effects, inhibiting transmembrane Na(+), K(+), Ca(2+), and slow L-type calcium channels, as well as its antiadrenergic effects. Unlike amiodarone, it has little effect at thyroid receptors (23). Dronedarone is a amiodarone analoge recently developed iodine-free compound (Sanofi Recherche), structurally related to amiodarone. Some early data, at least from animal work, suggests that dronedarone is less thyro-toxic and perhaps less pulmonary toxic. Rats were treated with amiodarone or dronedarone for 14 days with 100 mg/kg body weight and the expression of TRAlpha 1, TRAlpha 2, TRbeta 1 and several tri-iodothyronine (T3)-regulated genes was studied in the right atrium, LV wall and apex. The expression of TRAlpha 1, TRAlpha 2, TRbeta 1 and T3-regulated genes was studied using real-time PCR and non-radioactive in situ hybridisation. Both drugs affected TR expression in the right atrium similarly by decreasing TRAlpha 1 and beta 1 expression by about 50%. In the LV wall, both drugs decreased TRbeta 1 and, interestingly, only amiodarone increased TRAlpha 1. In the apex, amiodarone also increased TRAlpha 2. The changes seen in T3-dependent gene expression are reminiscent of foetal reprogramming. Both drugs have similar effects on the expression of thyroid hormone receptor isoforms in the right atrium of rats, which could partly contribute to their ability to decrease heart rate. On the other hand, the more profound effect of amiodarone appears on thyroid hormone receptor - and T3-dependent gene expression in the left ventricle wall suggests foetal reprogramming(24).

Dronedarone has a shorter half-life and can be loaded more easily than amiodarone. If indeed, dronedarone were less toxic, the fact that it can be

administered more rapidly would give it a distinct advantage. Clinical trials have to be completed to determine if these are true properties of the drug.

Dronedarone reduces renal creatinine and N-methylnicotinamide NMN clearance by about 18%, without evidence of an effect on glomerular filtration rate, renal plasma flow or electrolyte exchanges. This suggests a specific partial inhibition of tubular organic cation transporters. A limited increase in serum creatinine is therefore expected with dronedarone treatment, but does not mean there is a decline in renal function (25).

Antiarrhythmic pharmaceutical development for the treatment of AF is moving in several directions. Efforts are being made to modify existing agents, such as amiodarone, in an attempt to ameliorate safety and adverse effect concerns. (26). Dronedarone induces a marked reduction in sinus node automaticity, evidenced by decreases in spontaneous beating rate, AP amplitude, and slope of phase 4 depolarization. Isoproterenol dose-dependently increases sinus node automaticity in the presence of either amiodarone or dronedarone. Dronedarone resembled amiodarone in class III and sympatholytic effects, indicating its potential as a unique antiarrhythmic compound seemingly devoid of the side effects mediated by iodine in amiodarone.

Dronedarone prolong RR and QT intervals as a function of dose, without effect on circadian patterns. The relative prolongation of QT, QTc, and RR by dronedarone are significant. The QTc interval do not exhibit a clearly recognizable circadian pattern, suggesting that the circadian pattern of the QT interval is mostly a reflection of circadian changes in the RR interval (27). Dronedarone may be a useful antiarrhythmic alternative to amiodarone in the treatment of supraventricular arrhythmias(28). It is a new antiarrhythmic treatment of AF(26).Further studies are needed to better define dronedarone's safety profile and place in therapy(29). In two identical multicenter, double-blind, randomized trials, dronedarone (400 mg of the drug twice daily) was significantly more effective than placebo in maintaining sinus rhythm (SR) and in reducing the ventricular rate during recurrence of AF or flutter. Additionally, rates of pulmonary toxic effects and of thyroid and liver dysfunction were not significantly increased in the dronedarone group (30).

The DAFNE trial (31) The Dronedaronone Atrial Fibrillation Study After Electrical Cardioversion. This study was designed to determine the most appropriate dose of dronedarone for prevention of AF after cardioversion. It was the first prospective randomized trial to evaluate its efficacy and safety. The study concludes that dronedarone, at 800mg daily dose, appears to be effective and safe for the prevention of AF relapses after cardioversion. The absence of thyroid side effects and of proarrhythmia is important features of the drug.

The ATHENA trial(**A Trial With Dronedaronone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation**) is An Interventional, Prevention, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Efficacy Study multinational, trial evaluating the effects of dronedarone (400mg bid) compared with placebo, over a minimum 12-month follow-up period, in patients with AF or flutter. The trial is investigating the efficacy of dronedarone in preventing cardiovascular hospitalizations or death from any cause. The primary efficacy parameter is the combined endpoint of cardiovascular hospitalization and death. Secondary efficacy parameters are death of any cause, cardiovascular death, cardiovascular hospitalization and non-cardiovascular hospitalization. Enrolment was extended to 4300 patients in order to attain the planned rate of adverse events; patient recruitment is ongoing. Previously, Sanofi-aventis completed two pivotal phase III trials in AF.

The trials, EURIDIS Dronedaronone for the Maintenance of Sinus Rhythm (EUROpean trial In AF or flutter patients for the maintenance of SR)

American-Australian-African Trial with Dronedaronone in Atrial Fibrillation/Flutter Patients for the Maintenance of SR (ADONIS), dronedarone 400 mg b.i.d. showed significant efficacy against placebo in prevention of AF recurrence. The study involved 1237 patients who were in SR at the time of randomization. Results showed dronedarone to have anti-arrhythmic effects and a favorable benefit/risk ratio, with the absence of any proarrhythmic effect.

ERATO (Efficacy and safety of dronedARone for The cOntrol of ventricular rate), took place in 35 centres across nine European countries assessing dronedarone in 174 patients with permanent AF. Dronedaronone was in phase II trials in Japan for the treatment of AF; however, no recent developments have been reported.

ANDROMEDA trial raises safety concerns for patients with congestive heart failure and moderate to severe LV dysfunction. Dronedarone appears to be effective in preventing relapses of AF and atrial flutter.

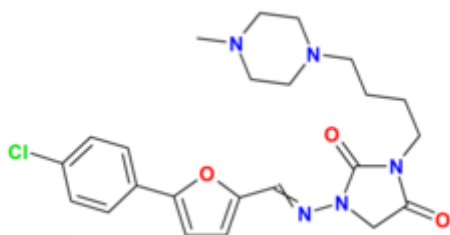
TdP the most severe adverse effect associated with amiodarone, has not yet been reported in humans with dronedarone. Dronedarone had little effect on thyroid function and hormone levels in animal models and had no significant effects on human thyroid function in clinical trials.

Dronedarone could be a useful drug for prevention of AF and atrial flutter relapses in low-risk patients. Further experimental studies and long-term clinical trials are required to provide additional evidence of efficacy and safety (32). Dronedarone works by blocking potassium, sodium, and calcium channels and exhibits antiadrenergic properties. The drug has been evaluated at doses of 400, 600, and 800 mg twice daily. It prolonged the time to AF recurrence to 60-158 days compared with 5-59 days with placebo and decreased heart rate during AF by 12-25 beats/min in clinical trials. Major adverse events include gastrointestinal side effects and risk of proarrhythmia. Dronedarone may increase the risk of mortality in patients with congestive heart failure(29).

Dronedarone and amiodarone display similar antiarrhythmic efficacy post-myocardial infarction, partly by preventing repolarization inhomogeneity. However, dronedarone increases bradyarrhythmic mortality possibly secondary to its negative inotropic effects (33).

### Azimilide dihydrochloride

**Structure:** 1-[[5-(4-chlorophenyl)-2-furyl]methylideneamino]-3-[4-(4methylpiperazin-1-yl)butyl]imidazolidine-2,4-dione



Azimilide

**Action mechanism** It is an investigational class III anti-arrhythmic drug that blocks fast(I<sub>Kr</sub>) and slow(I<sub>Ks</sub>) components of the delayed rectifier cardiac potassium channels. It is not approved for use in any country. Azimilide is a potassium blocker similar to dofetilide or sotalol, but it blocks both I<sub>Kr</sub> and I<sub>Ks</sub>. It does not perform as a beta-blocker like sotalol. Unlike sotalol, another class III antiarrhythmic drug, azimilide does not exhibit reverse-use dependence, that is, its binding characteristics and effectiveness are not related to the heart rate. azimilide permits once-daily dosing and limits major fluctuations in blood levels.

**Bioavailability:** Azimilide is 85% bioavailable, reaches peak blood concentrations in 6-8 h

Elimination: With a long exponential half-life of up to 4 days or 114 h. The drug is predominantly hepatically metabolized(34).

**Doses:** 75 or 125 mg daily

Clinical use Azimilide has been developed for treating both supraventricular and ventricular tachyarrhythmias. Azimilide showed a nonsignificant trend toward efficacy in maintaining SR in patients with AF(35). Azimilide did not demonstrate clinically important or statistically significant efficacy in reducing the risk for arrhythmia recurrence in patients with structural heart disease who were in atrial fibrillation and converted to sinus rhythm(36). A major randomized prospective placebo-controlled trial, AzimiLide post Infarct surVival Evaluation (ALIVE) was reported in the Highlights from the 2001 American Heart Association Scientific Sessions (37).

This trial evaluated the effect of 75 mg and 100 mg of azimilide on all-cause mortality in 3,717 recent myocardial infarction (MI) patients (5–21 days post-MI) at risk for SD. The major focus of the trial was on the 100-mg azimilide dose.

The primary objectives of ALIVE were to determine the effect of 100 mg azimilide on all-cause mortality in recent MI patients with a LV ejection fraction (LVEF) of 15–35%, and to evaluate a subgroup at presumed higher risk with low heart rate variability.

Using the intent to treat analysis, 1,690 patients received placebo and 1,691 received 100 mg azimilide. All-cause mortality was the same for both



groups. The patient dosing was initiated once daily in 73% of patients in-hospital and 27% out-of-hospital. Fewer patients in SR at baseline developed AF /flutter taking 100 mg azimilide (0.5%) compared with placebo (1.2%) ( $P = .04$ ).

The 100-mg and 75-mg azimilide doses have given a similar safety profile. For those patients who received 100 mg azimilide, serious adverse events and serious cardiovascular events occurred in 38.2% and 28.4%, respectively, and were similar with placebo (37.8% and 30.8%, respectively). The Event Committee classified five cases of torsade de pointes in the azimilide group (0.3%) compared with one patient receiving placebo (0.1%). The cases of torsade de pointes were associated with one or more risk factors, including age > 65 years, female gender, diuretic use, hypokalemia and/or hypomagnesemia or bradycardia.

Patients who received the 100-mg azimilide dose had severe neutropenia more frequently compared with those given placebo (0.9% vs. 0.2%). All cases of neutropenia occurred between 25 and 48 days in the azimilide group. No patients experienced life-threatening infections, and all patients recovered in 1–18 days, except 1 patient in whom a new myocardial infarction was associated with death.

In summary, azimilide given to high-risk, post-MI patients who had substantial LV dysfunction demonstrated no difference in all-cause mortality compared with placebo, and there appeared to be some positive effect on prevention of AF/flutter. Azimilide did not improve or worsen the mortality of patients after MI. Low HRV independently identified a subpopulation at high risk of mortality. Azimilide was safe and effective AF therapy in patients with depressed LV function after an MI (38).

There is a small increased risk in severe neutropenia, which occurs relatively early and is reversible.

FDA requires placebo controlled efficacy and safety studies as well as a mortality trial in patients with significant heart disease. Azimilide has completed these trials and passed these hurdles but almost all of the trials were outpatient. The FDA's preference appears to be to see what would occur in some in-patient

trials to verify under closer monitoring the apparent profiles seen so far in the outpatient trials.

Azimilide significantly reduced the recurrence of VT or VF terminated by shocks or antitachycardia pacing in ICD patients, thereby reducing the burden of symptomatic VT (39).

The anti-arrhythmic efficacy of azimilide is slightly superior to placebo but significantly inferior to sotalol in patients with persistent AF. The modest anti-arrhythmic efficacy and high rate of TdP and marked QTc prolongation limit azimilide utilization for the treatment of AF (40).

### **Side effects**

The most frequent reported side effect is headache, with rare serious adverse events of early reversible neutropenia and TdP. There is a small increased risk in severe neutropenia, which occurs relatively early and is reversible. Because the incidence of neutropenia occurred in such a small percentage, the FDA would like to see a greater number of patient exposures to verify that it is always early and reversible. That would allow them to develop appropriate inserts guidelines. Assuming all goes as expected, it will be 2004 before azimilide will be approved for use in the United States. If it is approved and not found to be associated with fatal neutropenia, then the once-daily outpatient dosing will give it a distinct advantage. It would fit into the algorithm alongside, or instead of, dofetilide in some circumstances.

Studies of azimilide for the treatment of AF show an overall incidence of TdP of only 0.5% (41). TdP is the most serious side effect and observed in patients with other predisposing factors, including hypokalemia. Azimilide-associated TdP has characteristics and risk factors similar to other Ikr blockers. However, there is a distinctive temporal profile. The TdP events are not concentrated in the first week. The azimilide-associated TdP rate is 1% and is not increased in patients with low LV ejection fraction, even in women(42).

### **Interactions**

Has not significant drug interactions with digoxin or warfarin. In animal models,

Coadministration of ciprofloxacin and azimilide could caused QT interval prolongation and episodes of TdP (43).

#### 4) IBUTILIDE

Ibutilide (Covert®) is a selective class III antiarrhythmic agent that when administered intravenously can terminate AF and atrial flutter. It is an antiarrhythmic medication that helps return the heart to its normal SR. Ibutilide reduces abnormal electrical signals that cause AF by stabilizing the heart muscle tissue. Ibutilide is given by IV. It acts for only a short period. The drug is used for the cardioversion of atrial flutter and AF, but it can cause TdP. Ibutilide is used to quickly convert AF to a SR. It is used as an alternative to electrical cardioversion or when electrical cardioversion or sedation is considered unsafe or inappropriate. Also, it is sometimes used to make electrical cardioversion more successful. The effectiveness of ibutilide depends on how long you have had AF and whether you have an underlying heart disease. The longer AF has been present, the less effective ibutilide is.

Amiodarone is also used for the cardioversion of AF and prolongs the QT interval but rarely causes TdP. Ibutilide is more effective than amiodarone in converting recent-onset atrial flutter to SR whereas both drugs are equally effective in converting recent-onset AF to SR (44).

In children and in patients with congenital heart disease with careful monitoring, ibutilide can be an effective tool in selected patients for cardioversion of atrial flutter (45).

During pregnancy direct current external cardioversion is the current method of terminating AF and atrial flutter. This technique is sometimes considered undesirable by both physician and patients due to the need for deep sedation or anesthesia. Ibutilide was used with success to terminate symptomatic persistent atrial flutter in a patient during her 24th week of pregnancy (46). The administration of amiodarone in the case of ibutilide failure may be a useful adjunct to current cardioversion protocols for recent onset AF (47).

Pharmacologic conversion of AF and atrial flutter has demonstrated conversion rates of 60% to 80%. Ibutilide is an excellent therapy option for restoring SR in the emergency department. Its use may obviate the need for admission, avoid the risks and inconveniences of general anesthesia to perform electrical cardioversion, and reduce the emergency department length of stay in selected patients with recent-onset atrial arrhythmias (48).

Ibutilide can be used for conversion of monomorphic atrial tachycardia with a similar efficacy as for AF, but with a considerably lower efficacy compared to typical atrial flutter (49). Although not essential for a successful outcome, pretreatment with ibutilide can lower energy requirements in transthoracic biphasic cardioversion. Cardioversion of AF with monophasic transthoracic shock is facilitated by pretreatment with ibutilide (50).

Ibutilide is effective for conversion of recent onset AF in patients presenting to the emergency department and there is a low rate of complications from ibutilide in this setting (51).

Intravenous Ibutilide is more effective than intravenous propafenone for the cardioversion of recent onset AF, and the adverse effects are rare and transient (52).

### **Side Effects:**

Ibutilide may cause many side effects. It should be used carefully, and you should be closely monitored for a minimum of 4 hours in the hospital after receiving ibutilide. Common side effects of Ibutilide are: Dizziness; headache; nausea; rapid heartbeat.

Side effects of ibutilide include:

- 1) Fast or Slow heartbeat.
- 2) Dizziness or lightheadedness.
- 3) Headache.
- 4) Sudden fainting.
- 5) Low blood pressure
- 6) Heart palpitations.

- 7) Rapid, uncontrolled heart rhythm: VT, Nonsustained monomorphic VT, (TdP) or VF.
- 8) Heart block
- 9) Heart failure
- 10) Nausea.
- 11) Shortness of breath.
- 12) Swelling of feet or ankles
- 13) Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue)

### **III) MISCELLANEOUS AGENTS**

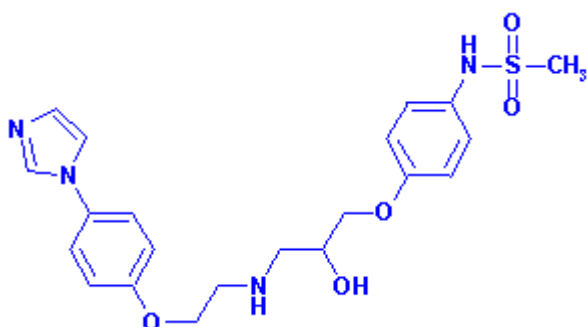
#### **6) Trecitilide**

is an analog of ibutilide that is orally effective. Its bioavailability is approx. 70%. It has a similar mechanism of action to ibutilide.

**7) Tedisamil (Pulzium®)** is a drug intended for cardiologists to treat AF and flutter, It is an innovative drug for now in the later phase of clinical development for treatment of rapid conversion of AF to normal SR. was originally developed as an antianginal agent. It blocks the delayed rectifier and transient outward potassium currents. Decreasing heart rate is potentially useful in ischaemic heart disease. Tedisamil is a bradycardic agent resulting from its ability to inhibit I(to) in atria. Tedisamil inhibits I(to), potassium current (IK), K(ATP) and the protein kinase A-activated chloride channel in ventricles as well as vascular IK and Ca(2+)-activated IK (IK((Ca))). Tedisamil prolongs cardiac APs and the QTc of the ECG and also increases cardiac refractoriness. The bradycardic effect of tedisamil is associated with a reduction in myocardial oxygen demand.

Diarrhea is a drawback to its further investigation.

#### **8) Ersentilide(CK-3579)**



It is a novel antiarrhythmic agent which combines blockade of the rapid component of the delayed rectifier potassium channel (IKr) with relatively weak beta-adrenergic blockade,

The combination of IKr and weak beta-adrenergic blockade, using ersentilide, represents a very effective and safe antiarrhythmic intervention able to overcome the limitations present in drugs devoid of any antiadrenergic effect. Such a combination may be very useful in the management of post-myocardial infarction patients at high arrhythmic risk.

### 9) Ambasilide

It is a class III antiarrhythmic, has been shown to block multiple cardiac channels including beta-adrenergic antagonism. Although the electrophysiological effects of ambasilide are characterized on the cellular level, its effects on an organ level have yet to be investigated. Ambasilide prolonged the RR, PQ, QRS, QT, and QTc in a concentration-dependent manner in either normal SR or with reduced heart rate (atriectomy).  $dP/dt_{min}$  was increased (became less negative) in the presence of increasing concentrations of ambasilide, whereas the vehicle produced less negative lusitropy. Ambasilide demonstrated use dependence by prolonging QTc less at slower heart rates (53).

### 10) Chromanol 293B

Chromanol 293B, trans-6-cyano-4-(N-ethylsulfonyl-N-methylamino)-3-hydroxy-2,2-dimethyl-chroman) is a lead compound of potential class III

antiarrhythmics that inhibit cardiac I(Ks) potassium channels. It is a relatively selective blocker of I(Ks) and the frequency dependence of APD prolongation caused by this IKs blocker is different from that caused by IKr blockade: 293B may be an interesting tool to study the physiologic role of IKs and the antiarrhythmic potential of IKs blockade. Drugs that selectively inhibit the I<sub>Ks</sub> are being considered as possible antiarrhythmic agents, because they produce more prolongation of APd at fast rates with less transmural dispersion of repolarization compared with blockers of I<sub>Kr</sub>. IKs are formed by the coassembly of KCNQ1 (Kv7.1, KvLQT1) and KCNE1 subunits (54).

Although the chromanol derivative chromanol 293B has been shown to be relatively selective in blocking I<sub>Ks</sub> in some species, its selectivity is far from established.

Pharmacological IKs block in the absence of sympathetic stimulation plays little role in increasing normal human ventricular muscle APd. However, when human ventricular muscle repolarization reserve is attenuated, IKs plays an increasingly important role in limiting AP prolongation(55).

IKs blockade significantly reduced HF-induced dispersion of repolarization to values seen in nonfailing hearts. By prolonging repolarization without increasing dispersion of repolarization, I(Ks) blockade may have antiarrhythmic effects without creating proarrhythmia(56).

## 11) Sematilide

Sematilide, a close structural analog of N-acetylprocainamide, prolongs cardiac APs in vitro, whereas it does not depress maximum AP upstroke slope, a "class III" action. It is a "pure" class III agent, that act largely by delaying conduction. The electrophysiologic profile of sematilide is consistent with selective block of outward potassium currents and associated isolated lengthening of the ventricular effective refractory period and APd.

Sematilide demonstrates a significant degree of reverse frequency-dependence of the ventricular APd and effective refractory period; and suppression of VT inducibility by sematilide appears to be correlated with increases in the right ventricular effective refractory period (57).

Wong et al report an evaluation of the clinical pharmacologic actions of sotalolol in 14 patients with chronic high-frequency nonsustained VT. In all, 36 intravenous infusions (range 0.15 to 1.5 mg/kg over 15 minutes) were administered in a dose-ranging, placebo-controlled study design.

Sotalolol sotalolol exerts class III actions in patients: prolonged QTc in a dose- and concentration-related fashion, did not alter PR or QRS, and slowed HR at high concentrations. The relations between dose and total area under the time-concentration curve, dose and peak plasma concentration, and peak plasma concentration and increase in QTc were linear. QTc increases of approximately equal to 25% were seen at plasma concentrations of approximately equal to 2.0 micrograms/ml. The mean elimination half-life was 3.6 +/- 0.8 hours, and most of a dose (77 +/- 13%) was recovered unchanged in the urine. Plasma concentrations greater than or equal to 0.8 micrograms/ml suppressed arrhythmias (5 patients) or aggravated them (3), including 1 patient who needed cardioversion for an episode of TdP (2.7 micrograms/ml) (58).

### **Treatment of TdP in aLQTS**

Treatment for TdP includes immediate defibrillation for hemodynamic instability. The patient with TdP who is in extremis should be treated with electrical cardioversion or defibrillation and the drug of Choice (Non-drug therapy): intravenous magnesium sulfate. Magnesium is usually very effective, even in the patient with a normal magnesium level. Intravenous MgSO<sub>4</sub> infusion effectively treated TdP in children with LQTS. Intravenous administration of magnesium sulphate (MgSO<sub>4</sub>) is a very effective and safe treatment TdP associated with acquired LQTS) in adults.

### **Alternatives**

- 1) Remove causative agents: Withdraw all QT-prolonging drugs. Potassium levels should be maintained in the high normal range, and all QT prolonging agents must be promptly discontinued;
- 2) Isoproterenol: to a rate of 90-100 bpm is effective.



- 3) Potassium (if hypokalemic) Treat hypokalemia if it is the precipitating factor and administer magnesium sulfate in a dose of 2-4 g intravenously (IV) initially.
- 4) A few cases of successful conversion using phenytoin and overdrive pacing have been reported.
- 5) Cervical sympathectomy and implantable pacemakers/defibrillators have been used in some cases for long-term management.

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