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Relationship among amiodarone, new class III antiarrhythmics, miscellaneous agents and acquired long QT syndrome

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Abstract

Class III drugs prolong the QT interval by blocking mainly the delayed rectifier rapid potassium outward current (IKr), with little effect on depolarization. This K^+ channel in encoded by the human ether-a-go-go-related gene (hERG). Inhibition of hERG potassium currents by class III antiarrhythmic drugs causes lengthening of cardiac action potential, which produces a beneficial antiarrhythmic effect. Excessive prolongation of the action potential may lead to acquired long QT syndrome, which is associated with a risk of "torsade de pointes". Class III agents can block all types of potassium channels: IKs, IKr, IKur and IK1. The main representing class III agent is amiodarone. It is the gold standard in the prevention of recurrence of atrial fibrillation. Although it is highly effective in treating many arrhythmias, large number of adverse effects limits its clinical use. Dronedarone is a synthetic amiodarone analogue, iodine-free compound, with fewer adverse effects, and shares amiodarone's multichannel blocking effects, inhibiting transmembrane Na+, IKs, IKur, IK1, and slow Ca^{++}L-type calcium currents. The main new generation class III drugs are: dofetilide, dronedarone, azimilide, and ibutilide. Oral dofetilide did not increase mortality in patients with a recent myocardial infarction or congestive heart failure. It is an alternative for the pharmacological conversion of atrial fibrillation and flutter. Azimilide blocks both rapid and slow potassium channels components. Azimilide is not a methanesulfonanilide compound. Trecitilide, tedisamil, ersentilide, ambasilide, chromanol and sematilide are class III miscellaneous agents. Old mixed agents are sotalol and bretylium. The present article reviews the main trials accomplished with these drugs. (Cardiol J. 2008; 14: 209–219)

Key words: antiarrhythmic drugs, sudden cardiac death, long QT syndrome

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Introduction

The list of drugs involved in the QT/QTc prolongation is continuously increasing. It is principally linked to a block of the outward potassium current IKr, with as a consequence a prolongation of the repolarization causing early after potentials and reentry. 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 IKr. The human ether-a-go-go-related gene (hERG) 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 torsade de pointes (TdP). A normal QTc interval does not exclude the risk of proarrhythmia [2]. Congenital long QT syndromes cause perturbation of ventricular repolarization causing QT prolongation on surface electrocardiogram (ECG). The aLQTS are caused mainly by drugs.

On the other hand, approximately 7.5% of caucasians are genetically lacking Cytochrome P450 CYP2D9 from their enzymatic system, which is necessary for the metabolization of drugs with the potential to cause QT interval prolongation. When they are administered and not properly metabolized, and concomitant with the genetic mutation of LQTS, the risk of events of TdP increases, since the half life of these drugs is extended. 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, and at last, there is an industrial risk for the manufacturer when a drug is withdrawn late when important quantities of money have already been invested for its development.

Other 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 sudden death. Drug-induced LQTS is characterized by a prolonged corrected QT interval (QTc) and increased risk of a polymorphic ventricular tachycardia (VT). 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 (IKr). 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 action potential. 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

Table 1. Class III antiarrhytmics.

I. Main representative agent
Amiodarone
II. New generation's agents
Dofetilide
Dronedarone
Azimilide
Ibutilide
III. Miscellaneous agents
Trecitilide
Tedisamil
Ersentilide
Ambasilide
Chromanol 293B
Sematilide
IV. Others old agents
Sotalol (combined class II/III)
Bretylium

Observation: In this manuscript we do not undertake group IV.

drugs can cause prolongation of repolarization in slowly depolarizing tissue or following a long compensatory pause, leading to repolarization disturbances and torsade de pointes.

Repolarization of cardiomyocytes is mainly performed by the rapid component of the delayed rectifier potassium current, IKr, which is encoded by hERG. Inhibition of hERG potassium currents by class III antiarrhythmic (Table 1) 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].

I. Main representative agent

Amiodarone

Although amiodarone is approved by the US Food and Drug Administration (FDA) 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). 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 (IKr) and slow (IKs) delayed outward potassium current (IK) 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 IK 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 IKs 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 numerous adverse effects limit [10–13] its clinical use. Adverse effects are common (more than 75% of patients receiving the drug) and increase after a year of treatment; some toxicities result in death. Half-life of 25–110 days can prolong toxicity.

II. New generation agents

Dofetilide

Structure. Dofetilide is a novel, highly specific class III methanesulfonanilide anti-arrhythmic drug.

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 works by selectively blocking the rapid component of the delayed rectifier outward potassium current (IKr). 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 AP duration. Dofetilide does not appear to interact with other cardiac ion channels, and this explains its minimal effects upon conduction velocity, myocardial

contractility and systemic hemodynamics. Unlike other antiarrhythmic agents, oral dofetilide did not increase mortality in patients with a recent myocardial infarction (MI) or congestive heart failure (HF), hence its importance as an alternative medication for the pharmacological conversion of AF and flutter, and maintenance of sinus rhythm (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.

Elimination. Renal and hepatic (CYP3A4 family). In patients with kidney disease higher blood levels may occur, which may increase the chance of side effects. Safety in severe liver disease is unknown.

Doses. For oral dosage form (capsules): adults — 125–500 μg two times a day.

Clinical use. Termination of supraventricular arrhythmia (prevention of recurrent AF or atrial flutter) and VT [increasing the electrical threshold for inducible VT/ventricular fibrillation (VF)]. Dofetilide is approved by the 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. 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.

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. 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. 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. In the 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% of 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.

Pregnancy. Dofetilide has not been studied in pregnant women. However, studies in animals have shown that dofetilide causes fetal 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 other drugs:

— antiarrhythmic or other cardiac medicine, such as amiodarone taken within the last 3 months or;
— antibiotics like macrolides or trimethoprim, alone or in combination with sulfamethoxazole (CYP3A4 family);
— bepridil;
— cimetidine;
— cisapride;
— megestrol;
— phenothiazines like prochlorperazine or trifluoperazine;
— tricyclic antidepressants like amitriptyline or desipramine;
— verapamil may cause irregular heartbeats;
— hydrochlorothiazide/triamterene may increase serum levels of dofetilide.

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 on thyroid receptors [23].

Dronedarone is an amiodarone analogue 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 [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 decrease in spontaneous heart 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 prolongs RR and QT intervals as a function of dose, without effect on circadian patterns. The relative prolongations of QT, QTc, and RR by dronedarone are significant. The QTc interval does 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 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 (Dronedarone Atrial Fibrillation Study after Electrical Cardioversion) [31]. 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 800 mg 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 are important features of the drug.

The ATHENA trial (A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation) is an interventional, prevention, randomized, double-blind, placebo controled, parallel assignment, efficacy multinational study, evaluating the effects of dronedarone (400 mg b.i.d.) 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 and non-cardiovascular hospitalization.

Previously, Sanofi-Aventis completed two pivotal phase III trials in AF. The trials, **EURIDIS** Dronedarone for the Maintenance of Sinus Rhythm (EURopean trial In AF or flutter patients for the maintenance of SR), American-Australian-African Trial with Dronedarone 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. Dronedarone 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.

Torsade de pointes, 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

Action mechanism. It is an investigational class III anti-arrhythmic drug that blocks fast (IKr) and slow (IKs) 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 IKr and IKs. 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 Evalution (**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 3717 recent 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 left ventricular 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, 1690 patients received placebo and 1691 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/atrial flutter taking 100 mg azimilide (0.5%) compared with placebo (1.2%, $p = 0.04$).

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/atrial flutter. Azimilide did not improve or worsen the mortality of patients after MI. Low heart rate variability (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].

Food and Drug Administration 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 implantable cardioverter defibrillator 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 usage 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 insert guidelines.

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 LVEF, even in women [42].

Interactions. Has no significant drug interaction with digoxin or warfarin. In animal models, coadministration of ciprofloxacin and azimilide could cause QT interval prolongation and episodes of TdP [43].

Ibutilide

Ibutilide 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 sinus rhythm.

Ibutilide reduces abnormal electrical signals that cause AF by stabilizing the heart muscle tissue. Ibutilide is given intravenously. 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.

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 60–80%.

Ibutilide is an excellent therapy option for restoring SR in the emergency department. Its use may obviate the need for admission, 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 patients should be closely monitored for a minimum of 4 h in the hospital after receiving ibutilide. Side effects of ibutilide include:

— fast or slow heartbeat;
— dizziness or lightheadedness;
— headache;
— sudden fainting;
— low blood pressure;
— heart palpitations;
— rapid, uncontrolled heart rhythm: VT, nonsustained monomorphic VT, TdP or VF;
— heart block;
— heart failure;
— nausea;
— shortness of breath;
— swelling of feet or ankles;
— severe allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips or tongue).

III. Miscellaneous agents

Trecitilide

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

Tedisamil

Tedisamil is a drug intended for cardiologists to treat AF and atrial flutter. It is an innovative drug for now in the later phase of clinical development for rapid conversion of AF to normal SR. It was originally developed as an antianginal agent. It blocks the delayed rectifier and transient outward potassium currents. Decreasing heart rate is potentially useful in ischemic 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.

Ersentilide

Ersentilide (CK-3579) 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.

Ambasilide

Ambasilide 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].

Chromanol 293B

Chromanol 293B is a lead compound of potential class III antiarrhythmics that inhibit cardiac IKs potassium channels. It is a relatively selective blocker of IKs 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 IKs 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 IKr. 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 IKs 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 AP duration. 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, IKs blockade may have antiarrhythmic effects without creating proarrhythmia [56].

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, which acts largely by delaying conduction. The electrophysiologic profile of sematilide is consistent with the selective block of outward potassium currents and associated isolated lengthening of the ventricular effective refractory period and AP duration.

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

Sematilide exerts class III actions in patients: prolongs QTc in a dose- and concentration-related fashion, does not alter PR or QRS, and slows heart rate 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 μg/mL. The mean elimination half-life was 3.6 ± 0.8 h, and most of a dose (77 ± 13%) was recovered unchanged in the urine. Plasma concentrations greater than or equal to 0.8 μg/mL suppressed arrhythmias (5 patients) or aggravated them (3 patients), including 1 patient who needed cardioversion for an episode of TdP (2.7 μg/mL) [58].

Treatment of torsade de pointes in acquired long QT syndrome

Treatment of 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: intravenous magnesium sulfate. Magnesium is usually very effective, even in the patient with a normal magnesium level. Intravenous $MgSO_4$ infusion effectively treated TdP in children with long QT syndrome.

Intravenous administration of magnesium sulphate ($MgSO_4$) is a very effective and safe treatment for TdP associated with acquired LQTS in adults.

Alternatives

1. Withdraw causative agents is a very important conduct. Potassium levels should be maintained in the high normal range.
2. Isoproterenol: to a rate of 90–100 bpm is effective.
3. Potassium (if hypokalemic): treat hypokalemia as if it is the precipitating factor and administer magnesium sulfate in a dose of 2–4 g intravenously 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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