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Azimilide Decreases Recurrent Ventricular Tachyarrhythmias in Patients With Implantable Cardioverter Defibrillators

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OBJECTIVES This study evaluated the effects of azimilide dihydrochloride (AZ) on anti-tachycardia pacing (ATP) and shock-terminated events in patients with implantable cardioverter defibrillators (ICDs).

BACKGROUND Animal studies have shown the effectiveness of AZ for therapy of supraventricular and ventricular tachycardia (VT). Azimilide dihydrochloride was investigated as adjunctive treatment for reducing the frequency of VT and, thus, the need for ICD therapies, including ATP and cardioversion/defibrillation (ICD shocks) in patients with inducible monomorphic VT.

METHODS A total of 172 patients were randomized to daily treatment with placebo, 35 mg, 75 mg, or 125 mg of oral AZ in this dose-ranging pilot study of patients with ICDs. The majority of patients had a history of documented remote myocardial infarction and congestive heart failure New York Heart Association class II or III.

RESULTS The frequency of appropriate shocks and ATP were significantly decreased among AZ-treated patients compared with placebo patients. The incidence of ICD therapies per patient-year among the placebo group was 36, and it was 10, 12, and 9 among 35 mg, 75 mg, and 125 mg AZ patients, respectively (hazard ratio = 0.31, p = 0.0001). Azimilide dihydrochloride was generally well tolerated and did not affect left ventricular ejection fraction or minimal energy requirements for defibrillation or pacing.

CONCLUSIONS Azimilide dihydrochloride may be a safe and effective drug for reducing the frequency of VT and ventricular fibrillation in patients with implanted ICDs. (J Am Coll Cardiol 2004;43: 39–43) © 2004 by the American College of Cardiology Foundation

Azimilide dihydrochloride (AZ) is a novel antiarrhythmic that blocks rapid (IKr) and slow (IKs) (1) components of the delayed rectifier cardiac potassium channels. The mechanisms of action of AZ result in a rate independent class III (Vaughan-Williams) effect in humans (2–4) and decreased minimum energy requirements for defibrillation in animal studies (5). Azimilide dihydrochloride was effective and generally well tolerated in patients with supraventricular arrhythmia (6). The implantable cardioverter defibrillator (ICD) is the treatment of choice for patients with life-threatening ventricular tachyarrhythmias, and antiarrhythmics have become increasingly more important as adjunctive therapy for these patients. In fact, concomitant administration of antiarrhythmic drugs may be as high as 70% in patients with ICDs (7). The use of antiarrhythmic drugs with ICDs reduces the frequency of atrial fibrillation, reduces sustained and non-sustained ventricular tachycardia (VT), and improves the control of maximal sinus rate (8). These beneficial effects of antiarrhythmics are achieved more frequently by slowing VT rates and allowing termination by anti-tachycardia pacing (ATP) rather than by preventing fast VT-triggered shocks (7). Therefore, the efficacy of a concomitant antiarrhythmic therapy for patients with ICDs should be evaluated by its ability to affect frequencies of shocks and ATP (9). In this study we investigated the effects of AZ on ATP and shock-terminated events in patients with ICDs.

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METHODS

A double-blind, placebo-controlled, pilot study of 172 patients with ICDs, recruited from 37 centers in the U.S., was initiated to determine the effect of AZ on the recurrence of ICD therapies (shocks and ATP) in patients with documented VT at electrophysiologic study. Patients were randomly assigned to receive either 35 mg, 75 mg, or 125 mg of oral AZ or placebo with stratification according to left

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Abbreviations and Acronyms

AE = adverse event
ATP = anti-tachycardia pacing
AZ = azimilide dihydrochloride
EGM = electrogram
HR = hazard ratio
ICD = implantable cardioverter defibrillator
IKr = rapid component of cardiac potassium channels
IKs = slow component of cardiac potassium channels
LVEF = left ventricular ejection fraction
PVC = premature ventricular contraction
TdP = Torsade de Pointes
VF = ventricular fibrillation
VT = ventricular tachycardia

ventricular ejection fraction (LVEF). Institutional review board approval and written informed consent were obtained before starting the study.

Patients were included in this study if they met one of the following criteria: 1) an ICD implantation had occurred 30 days or more before randomization, and the patient had at least one ICD shock within the preceding year; or 2) an ICD had been implanted for symptomatic VT within 30 days of randomization, and the patient had an inducible sustained monomorphic VT. In this case, patients were required to have documented monomorphic VT or ventricular fibrillation (VF) and to have an inducible VT or VF upon non-invasive, programmed stimulation with an implanted ICD. A baseline electrophysiologic study was required, with induction and termination of VT with up to three extrastimuli at cycle lengths of 600 and 400 ms.

Patients were excluded if they: 1) were <18 years of age; 2) had class IV, New York Heart Association heart failure; 3) were taking class I or class III antiarrhythmic agents; 4) had unresolved angina pectoris or had experienced a myocardial infarction within 90 days of randomization; 5) had QTc longer than 440 ms or JTc >320 ms (if QRS >120 ms); 6) had a history of polymorphic VT, including Torsade de Pointes (TdP); 7) had hypertrophic cardiomyopathy or restrictive heart disease; 8) were hemodynamically unstable; or 9) had clinically significant liver or renal dysfunction.

Patients were randomly assigned to receive 35 mg, 75 mg, or 125 mg of oral AZ or placebo. All patients were evaluated at week 2 and months 1, 3, 6, 9, and 12 after the administration of AZ or placebo during which the following safety assessments were made: 1) 12-lead electrocardiogram (ECG); 2) physical examination with adverse event (AE) assessment; and 3) clinical laboratory parameter assessments. A 24-h ECG recording was obtained at baseline and at the month-1 visit. A two-dimensional echocardiographic assessment of LVEF was obtained at baseline and at the month-6 visit. Non-invasive electrophysiologic testing to determine minimal energy requirement for defibrillation was performed at baseline and at the month-1 visit. The ICD was interrogated at every visit, and stored electrograms (EGMs) were retrieved. All patients were evaluated after a documented ICD shock.

Appropriate ICD shock or ATP was defined as any ICD therapy that occurred in response to a VT or VF retrieved on stored EGMs. An events committee, composed of four electrophysiologists, reviewed the blinded EGM data and classified all arrhythmic events requiring ICD therapies. Events were classified by an agreement of two reviewing electrophysiologists. If there was a disagreement between the two electrophysiologists, the tie was broken by a third electrophysiologist. If no agreement could be reached, the entire committee reviewed the disputed event until a consensus could be achieved. If a consensus was not possible, the majority opinion prevailed as the final interpretation.

Statistical methods. The Andersen-Gill proportional hazards model (10) was used to analyze recurrent ICD therapies. This model used all the ICD therapies that the patients experienced during the follow-up period. In this analysis, only tachycardia detections requiring appropriate shock or ATP therapy were used. The Andersen-Gill analysis was performed using SAS statistical software, Proc Phreg, version 8.2 (SAS Institute, Cary, North Carolina).

In addition, an approximation of the log-rank test (11) was used to compare the ICD therapy rate (incidence) per patient-year exposure across treatment groups. This test is a form of a simple chi-square test. It is used to compare VT incidence between the groups. The test uses the reciprocal of the total VT events for each treatment group as a function of the variance of the test. This type of statistical analysis is particularly useful in this instance because multiple VT events are experienced by some patients.

All appropriate ICD therapies were analyzed. Arrhythmia episodes requiring multiple therapy deliveries to terminate were considered a single event detection. Patients who withdrew before completion of 374 days of the study follow-up had their efficacy measure censored on the day of the withdrawal.

RESULTS

Overall, 172 patients were randomized in this study, with 37 patients receiving placebo, 44 patients receiving 35 mg AZ, 45 patients receiving 75 mg AZ, and 46 patients receiving 125 mg AZ. Data from all 172 patients were included in the statistical analysis. Most of the patients were followed up for 374 days with the mean (±SD) follow-up of 279 ± 143, 259 ± 156, 285 ± 136, and 247 ± 158 days for placebo, 35 mg, 75 mg, and 125 mg, respectively. A total of 2,011 appropriate ICD therapies were detected in this study, with a mean number of therapies per patient of 18 ± 50 and a median of 4. A total of 358 appropriate ICD shocks were detected, with a mean number of shocks per patient of 4 ± 5 and a median of 2. Demographic and baseline cardiac characteristics are presented in Table 1.

The majority of patients had an LVEF <35% (62%) with no significant differences among the treatment groups. The

Table 1. Demographic and Baseline Cardiac Characteristics

Characteristics	Placebo (n = 37)	Azimilide Dihydrochloride 35 mg (n = 44)	75 mg (n = 45)	125 mg (n = 46)
Male	31 (84%)	41 (93%)	41 (91%)	41 (89%)
Age (yrs)*	65 (11)	69 (9)	64 (10)	65 (13)
LVEF (%)*	34 (14)	31 (11)	28 (12)	30 (14)
LVEF <35%	19 (51%)	26 (59%)	32 (71%)	29 (63%)
Heart rate (beats/min)*	74 (15)	70 (16)	70 (13)	73 (15)
QRS interval (ms)*	132 (34)	130 (32)	133 (29)	131 (31)
QTc value (ms)*	419 (20)	416 (21)	416 (15)	420 (28)
JTc value (ms)*	296 (23)	288 (31)	304 (35)	294 (19)
Previous MI	30 (81%)	34 (77%)	37 (82%)	38 (83%)
Diabetes	10 (27%)	6 (14%)	10 (22%)	13 (28%)
No CHF	9 (24%)	12 (27%)	10 (22%)	14 (30%)
NYHA class				
I	15 (41%)	15 (34%)	16 (36%)	9 (20%)
II	12 (32%)	15 (34%)	13 (29%)	19 (41%)
III	1 (3%)	2 (5%)	6 (13%)	4 (9%)
Concomitant medications during the study				
Beta-blockers	16 (43%)	14 (32%)	22 (49%)	20 (44%)
ACE inhibitors	29 (78%)	35 (80%)	40 (89%)	32 (70%)
Diuretics	30 (81%)	32 (73%)	31 (69%)	33 (72%)
Calcium channel blockers	11 (30%)	12 (27%)	13 (29%)	12 (26%)

*Data shown are mean and SD.

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; n = number of patients; NYHA = New York Heart Association.

percentage of patients who withdrew from the study voluntarily was equally distributed among the treatment groups. No differences were observed in blood pressure, heart rate, or ECG variables. The use of concomitant medication was similar among the groups.

AEs. The overall proportion of patients who reported AEs was similar across all groups and is presented in Table 2.

Forty patients were withdrawn from the study because of AEs, seven (19%) from placebo, and 33 (24%) from AZ groups, overall. No differences were detected between the placebo and AZ patients in the number of AEs that the investigators considered drug related. The majority of the reported serious AEs were cardiovascular. There were three reported episodes of TdP in two patients (1 male and 1 female). Both patients were receiving 125 mg of AZ. In one patient, TdP occurred after a short duration of exposure to AZ, and in both patients it occurred within the context of ongoing myocardial ischemia.

Effects of AZ on frequency of VT and VF. Azimilide dihydrochloride significantly reduced the frequency of appropriate ICD therapies (shocks and ATP-triggered by VT/VF) at all administered doses by 69%, compared with placebo (hazard ratio [HR] = 0.31, p = 0.0001, Table 3), without affecting pacing or defibrillation or pacing thresholds (Table 4). In addition, AZ significantly reduced the frequency of VTs and the requirement for ATP therapies by 66% to 79% (HR range = 0.21 to 0.34, p = 0.0001, Table 3).

A dose-dependent reduction of VT frequency is paralleled by a similar trend in reduced frequency of premature

Table 2. Adverse Events for All Randomized Patients

	Placebo	35 mg AZ	75 mg AZ	125 mg AZ
Number of patients randomized	37	44	45	46
Mean number of AEs per patient	5.9	4.5	6.2	6.0
Number (%) of patients with SAEs	17 (46%)	23 (52%)	20 (40%)	19 (41%)
Number of deaths	3 (8%)	1 (2%)	1 (2%)	0 (0%)
Number of patients with TdP	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Number of patients with new or exacerbation of VT reported as AE	9 (24%)	6 (14%)	8 (18%)	5 (11%)
Number of patients withdrawn for any reason	13 (35%)	18 (41%)	18 (40%)	22 (48%)
Number of patients withdrawn due to AEs	7 (19%)	10 (23%)	9 (20%)	14 (30%)
Number of patients with "drug-related" AEs	14 (38%)	14 (32%)	16 (36%)	17 (37%)
Number of patients hospitalized	16 (43%)	23 (52%)	20 (44%)	19 (41%)

*All the comparisons between placebo and AZ patients were not statistically significant (p > 0.05).

AE = adverse event; ATP = anti-tachycardia pacing; AZ = azimilide; SAE = serious adverse event; TdP = Torsade de Pointes; VT = ventricular tachycardia.

Table 3. ICD Therapy Analysis

ITT Analysis: All Appropriate ICD Therapies (Shocks and ATP)					
Treatment	**n**	**Hazard Ratio (95% CI)**	**p Value (AG Model)**	**Incidence per Pt-Year (95% CI)**	**p Value (Log-Rank)**
Placebo	37			36 (34, 38.4)	
35 mg AZ	44	0.31 (0.28, 0.36)	0.0001	10 (8.9, 11.1)	<0.0001
75 mg AZ	45	0.31 (0.27, 0.34)	0.0001	12 (10.8, 13)	<0.0001
125 mg AZ	46	0.31 (0.27, 0.36)	0.0001	9 (7.8, 9.8)	<0.0001
Analysis of Frequency of Appropriate ATP Therapies					
Treatment	**n**	**Hazard Ratio (95% CI)**	**p Value (AG Model)**	**Incidence per Pt-Year (95% CI)**	**p Value (Log-Rank)**
Placebo	29			42.1 (39.4, 44.8)	
35 mg AZ	35	0.26 (0.23, 0.31)	0.0001	9.1 (7.9, 10.3)	<0.0001
75 mg AZ	31	0.34 (0.30, 0.39)	0.0001	13.8 (12.3, 15.3)	<0.0001
125 mg AZ	36	0.21 (0.18, 0.25)	0.0001	6.8 (5.7, 7.9)	<0.0001

AZ = azimilide; AG = Andersen-Gill model of proportional hazards for frequency of appropriate ATPs in patients with ATP therapy programmed "on" at any time during the study; ATP = antitachycardia pacing; CI = confidence interval; ICD = implantable cardioverter defibrillator; Pt = patient.

ventricular contractions (PVCs) (Table 4). Of particular importance is the observation that there was no significant impact on LVEF, resting heart rate, or systemic pressure, suggesting that AZ does not adversely affect cardiac function or hemodynamic variables in a very sick population of patients (i.e., patients with impaired left ventricular function). A modest dose-dependent increase in QTc/JTc intervals was noted, consistent with the anticipated action of an IKr and IKs channel-blocking antiarrhythmic drug.

DISCUSSION

This dose-ranging study was conducted to test the effect of AZ on the frequency of recurrent VT and VF. Recurrent ICD therapies are documented and stored by the ICDs and can therefore be easily retrieved, diagnosed, and validated as a measure of antiarrhythmic drug efficacy in this patient population. Because all patients are protected from sudden cardiac death by the implanted ICDs, the relative reduction in frequency of documented ICD therapies is an effective surrogate measure of the antiarrhythmic drug efficacy for VT and VF suppression.

Azimilide dihydrochloride caused a significant reduction in the delivery of all appropriate programmed ICD therapies. Previous studies with antiarrhythmic drugs in patients with ICDs have reported the reduction of VT terminated by ICD shocks (12,13). In the present study, we observed a similar decrease in the occurrence of all appropriate ICD therapies, both shocks and ATP triggered by VT/VF. A dose-related decrease in PVC frequency in the 24-h ECG data collected 30 days after dose initiation was also observed. However, a clear dose response was not observed regarding frequency of shocks and ATP. A lack of clear separation is probably related to a relatively small sample size among study groups.

Decreasing the recurrence of ICD therapies triggered by VT/VF is clearly beneficial in the light of the well-documented discomfort of ICD shocks, the worsening of heart failure secondary to frequent VTs and resultant therapies (ATP and shocks), and the negative psychological impact of recurrent shocks, as well as other quality of life issues (14–18). On a practical level, reducing the number of inappropriate ICD therapies would also be expected to enhance ICD longevity by conserving the battery drain (19).

Azimilide dihydrochloride was generally well tolerated. No statistical differences were observed between placebo and AZ patients among safety parameters reported in Table 2. Mortality was low and unrelated to tachyarrhythmic events or drug-related AEs. Three episodes of TdP in two

Table 4. Median Percent Change From Baseline* (p Value)†

	Placebo (n = 37)	**35 mg (n = 44)**	**75 mg (n = 45)**	**125 mg (n = 46)**
Heart rate (beats/min)	−1.0	−2.8 (0.95)	−4.2 (0.68)	−3.9 (0.82)
QTc/JTc (ms)	−3.0	0.98 (0.27)	2.5 (0.31)	8.7 (0.02)
(PVC/24 h)	28%	−24% (0.04)	−38% (0.02)	−66% (0.003)
Systolic BP	2.1	0.0 (0.30)	−1.5 (0.45)	−3.0 (0.03)
Diastolic BP	−1.2	−1.2 (0.95)	2.9 (0.61)	−6.7 (0.16)
LVEF (%)‡	−1.5	1.9 (0.72)	7.4 (0.26)	5.9 (0.31)
mDFE (J)‡	1.2	−1.0 (0.06)	−0.1 (0.32)	0.8 (0.92)
mPE (V)‡	0.6	0.5 (0.11)	−0.3 (0.10)	−0.4 (0.60)

*Change from baseline to month 1 visit; †Wilcoxon rank-sum test; ‡Represents mean % change from baseline.
BP = blood pressure; LVEF = left ventricular ejection fraction; mDFE = minimal defibrillation energy; mPE = minimal pacing energy; PVC = premature ventricular contractions percent.

patients were effectively treated by the ICD without adverse consequences. In both patients ischemia appeared to be the immediate trigger.

Hemodynamic status was not affected by AZ treatment, and results observed in this study (Table 3) were consistent with results from previous studies with similar doses conducted in patients with supraventricular tachyarrhythmias (20).

Clinical implications. Significant decrease in the ICD therapies (shocks and ATP), associated with a generally favorable AE profile, suggests that AZ may have an important role to play as adjunctive therapy for patients with ICDs in the reduction of VT/VF that leads to recurrent ICD therapies. A larger study called Shock Inhibition Evaluation with AzimiLiDe (SHIELD) is underway to confirm the findings of this pilot study.

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APPENDIX

For a complete list of clinical investigators who provided and cared for study patients, please see the January 7, 2004, issue of *JACC* at www.cardiosource.com/jacc.html.