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Azimilide

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Contents

Abstract

▲ Azimilide is a potassium channel antagonist that, in contrast to existing class III antiarrhythmic agents, blocks both the rapidly (I_{Kr}) and slowly (I_{Ks}) activating components of the delayed rectifier potassium current.

▲ In animal and clinical studies, azimilide prolonged repolarisation by increasing the action potential duration and effective refractory period. In animal models, azimilide was effective in terminating both atrial and ventricular arrhythmias. Azimilide also demonstrated antifibrillatory efficacy in a canine model of sudden cardiac death.

▲ In patients with a history of atrial fibrillation/flutter, oral azimilide controlled arrhythmias more effectively than placebo in a 6-month randomised double-blind study. At a dosage of 125mg once daily, azimilide significantly increased the time to first symptomatic recurrence of atrial fibrillation/flutter. However, no significant difference between placebo and azimilide was found in another study.

▲ Oral azimilide 100mg once daily demonstrated clinically significant treatment effects in patients with paroxysmal supraventricular tachycardia.

▲ In clinical trials, azimilide was generally well tolerated and headache was the most commonly occurring adverse event. Azimilide is associated with a low incidence of proarrhythmic events, such as torsades de pointes, and few serious adverse events have been reported.

Features and properties of azimilide (NE-10064)	
Indications	
Supraventricular arrhythmias	Clinical trials
Postmyocardial infarction	Clinical trials
Mechanism of action	
Class III antiarrhythmic	Potassium channel antagonist. Prolongs repolarisation by blocking I_{Kr} and I_{Ks}
Dosage and administration	
Usual dosage in clinical trials	100 to 125mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (150mg)	
Peak plasma concentration	191 μg/L
Time to peak plasma concentration	5.2 to 5.6h
Clearance	0.15 L/h/kg
Elimination half-life	4 to 5 days
Adverse events	
Most frequent	Headache
Serious events	Low incidence of torsades de pointes

Azimilide (molecular weight 530.88)

Azimilide is a class III antiarrhythmic agent and, as such, prolongs the cardiac action potential duration and effective refractory period. Drugs of this class often exhibit reverse rate-dependent activity. This term describes the prolongation of action potential duration at normal heart rates (HR) and the decline in the magnitude of prolongation as heart rate increases. Thus, these agents may lose efficacy at the high heart rates which may be achieved during tachyarrhythmias.[1] These reverse rate-dependent characteristics may be related to differential blockade of the rapidly (I_{Kr}) and slowly (I_{Ks}) activating components of the delayed rectifier potassium current (I_K). Isolated blockade of I_{Kr} has maximal efficacy at slower heart rates, and the progressive contribution of IK_s to repolarisation as heart rate increases overcomes IK_r blockade, resulting in no further effect on action potential prolongation.[2] In contrast to existing class III agents (including sotalol and dofetilide) which have little or no inhibitory effect on I_{Ks},[2,3] azimilide blocks both components of I_K.[4-7]

1. Pharmacodynamic Profile

Mode of Action

- Voltage clamp studies in cardiac tissues from several species show that azimilide reversibly blocks I_{Kr} and I_{Ks} with concentrations producing half maximal inhibition (IC_{50}) of 0.1 to 0.4 μmol/L and 0.7 to 3 μmol/L, respectively. In guinea-pig ventricular myocytes, in which the majority of studies were performed, the effects of azimilide on I_{Ks} were generally time-, voltage- and weakly rate-dependent.[8] Experience in human isolated atrial and ventricular myocytes provided evidence that azimilide inhibits I_{Kr} and I_{Ks} in a concentration-dependent manner.[9] Azimilide also has inhibitory effects on the inward sodium current and L-type calcium current at concentrations higher (>5- and 10-fold, respectively) than those that block I_{Ks}.[5,6,10,11]

- Radioligand binding studies have indicated that azimilide has affinity for α- and β-adrenergic, muscarinic and 5-HT receptors in rat brain membranes.[12] However, studies in anaesthetised rats have demonstrated that azimilide has no β-adrenergic antagonist effects at antifibrillatory doses.[13]

- Blockade of potassium currents by azimilide prolongs repolarisation. This effect manifests as an increase in action potential duration and effective refractory period, and has been demonstrated in various *in vitro* preparations including guinea-pig ventricular myocytes and ferret isolated papillary muscle. In these models, azimilide was found to have weak reverse rate-dependent effects on action potential duration and effective refractory period.[5,14]

- Infusion of azimilide 0.6 mg/kg/min to a cumulative maximum of 54 mg/kg in 5 anaesthetised open-chest dogs significantly ($p < 0.05$) increased the heart rate-corrected QT interval (QT_c) to a maximum of 34% above baseline at a dose of 8.9 mg/kg. At this dose, mean arterial pressure (MAP) and -dP/dt were unchanged, heart contractile force and +dP/dt were significantly increased (10% and 34%, respectively), and HR decreased by 12%. At higher doses, significant reductions in HR, MAP, +/-dP/dt and contractile force were observed.

Azimilide had no effect on PR or QRS intervals, left ventricular end diastolic pressure, cardiac output, stroke volume or total peripheral resistance at any dose.[15]

- In 5 conscious dogs, oral (30 mg/kg) and intravenous (10 to 15 mg/kg) azimilide increased the ventricular effective refractory period by up to 18% without affecting conduction time. In contrast to *in vitro* findings, this effect was rate-independent, being observed at both low and high heart rates.[16]

Antiarrhythmic Effects in Animal Models

- In a canine model of sustained vagal-stimulated atrial fibrillation, the efficacy of intravenous azimilide was compared with that of dofetilide. Overall, azimilide 10 or 20 mg/kg was 93% effective (13 of 14 animals) in terminating arrhythmias. A pharmacologically equivalent dose of dofetilide (0.16 mg/kg) terminated atrial fibrillation in 50% of animals (6 of 12). Both drugs produced significant ($p < 0.001$) prolongations of the atrial effective refractory period. While dofetilide showed reverse use-dependent effects on the effective refractory period, the effects of azimilide were rate-independent.[17]

- In a canine sterile pericarditis model, intravenous azimilide 10 mg/kg terminated electrically induced atrial flutter in 100% of animals and prevented arrhythmia reinduction in 4 of 8 dogs. At a dose of 30 mg/kg, reinduction was completely prevented.[18] Similarly, in a surgically induced (atrial lesion) re-entry model, intravenous azimilide 2 to 11.7 mg/kg terminated atrial flutter in all trials (n = 8 dogs). In this study, sotalol (6.85 ± 1.04 mg/kg) terminated atrial flutter in only 3 of 5 trials (n = 4 dogs).[19]

- In a further canine model, intravenous azimilide (cumulative doses of 1 to 30 mg/kg) was effective in preventing the induction of ventricular arrhythmias using programmed electrical stimulation (PES) 4 to 6 days after surgical myocardial infarction. Azimilide prevented arrhythmias in 5 of 9 inducible dogs, including 2 animals with ventricular fibrillation, 2 with sustained ventricular tachyarrhythmia and 1 with nonsustained ventricular tachyarrhythmia. In comparison, sotalol (0.3 to 10 mg/kg) was effective in all 5 dogs tested, although 3 were reinducible at doses higher than the effective dose. Azimilide increased left ventricular refractoriness in normal and infarcted zones, as evidenced by increases of up to 36% and 31% in the effective refractory period and QT_c, respectively.[20]

- A second study using this model compared the efficacy of intravenous azimilide 3 to 30 mg/kg with that of dofetilide 10 to 100 μg/kg in 4-day postinfarct dogs with PES-induced sustained ventricular tachyarrhythmia or nonsustained ventricular tachyarrhythmia. Azimilide suppressed ventricular tachyarrhythmia in 50% of animals (5 of 10), while dofetilide was effective in 2 of 7 animals (28%).[21]

- In a further study, intravenous azimilide 10 mg/kg significantly reduced the incidence of PES-induced ventricular tachycardia in 4 of 12 dogs 3 to 5 days after surgically induced myocardial infarction. In contrast, 11 of 12 animals remained inducible after vehicle administration. Overall, azimilide significantly ($p < 0.05$) reduced the incidence of PES-induced ventricular tachycardia compared with vehicle-treated controls.[22] This study also investigated the effects of azimilide on ischaemia-induced ventricular fibrillation using a model of sudden cardiac death (secondary site, thrombus-induced occlusive ischaemic event within 7 days of the primary infarction). Azimilide afforded 75% protection against sudden cardiac death during the first hour after onset of ischaemia, compared with 25% in vehicle-treated dogs ($p = 0.018$, n = 12 per group) [fig. 1]. The antifibrillatory efficacy of azimilide remained superior to that of vehicle after 14 hours (58% *vs* 14% survival; $p = 0.040$).[22]

- Intravenous azimilide (1 to 18 mg/kg) had dose-dependent antiarrhythmic efficacy in a rat coronary artery ligation/reperfusion model. Ventricular fibrillation was partially (≥67%) or completely

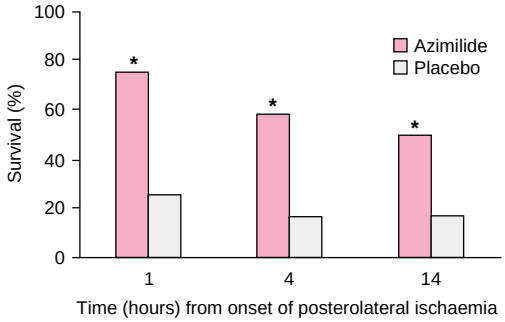

Fig. 1. Protection against ischaemia-induced ventricular fibrillation in a canine model of sudden cardiac death. Percentage survival of animals treated with intravenous azimilide 10 mg/kg or placebo (n = 12, both groups) after posterolateral ischaemia, induced within 7 days of a previous anterior myocardial infarction; * $p < 0.05$ *vs* placebo.[22]

suppressed at all doses. Dofetilide 0.3 to 18 mg/kg and sotalol 0.01 to 10 mg/kg provided 33% to 100% protection against ventricular fibrillation. Azimilide 18 mg/kg also demonstrated efficacy in suppressing ventricular extrasystoles and ventricular tachyarrhythmia in 1 of 4 and 3 of 4 animals, respectively. While dofetilide had no effect on these parameters at the doses tested, the highest dose of sotalol afforded protection against ventricular extrasystoles (1 of 6 animals) and ventricular tachycardia (2 of 6). Azimilide produced significant ($p < 0.05$) reductions in HR at all doses but produced differential effects on MAP. Significant increases were observed at doses of 0.56 and 1 mg/kg (+10% and +27%, respectively), while at higher doses (10 and 18 mg/kg) MAP was significantly reduced (–1% and –6%, respectively).[23]

• Transient premature ventricular contractions, ventricular tachycardia and torsades de pointes have been reported during azimilide treatment in certain canine models of stimulated arrhythmia.[21,22,24] However, in a rabbit model of proarrhythmia, azimilide showed less proarrhythmic potential than other class III agents such as dofetilide and sotalol. Drugs were administered at pharmacologically equivalent doses that increased QT_c by 20%.[25]

Electrocardiographic Studies in Humans

• The effects of a single oral dose of azimilide 0.2 to 8 mg/kg or placebo on electrocardiographic parameters were investigated in volunteers. At the highest dose, a 32% increase in QT_c (a marker of class III antiarrhythmic activity) was observed 12 hours after administration. However, no significant effects on the PR and QRS intervals or haemodynamic parameters (HR and blood pressure) were noted.[26]

• In a 14-day randomised placebo-controlled study involving 119 individuals, azimilide (35, 100, 150 or 200mg) was administered orally as a twice daily loading dose for 1, 2 or 3 days, followed by daily maintenance dosages. A dose-dependent prolongation in QT_c interval was observed. Azimilide 100mg produced an average maximum increase compared with baseline of 12.4 to 14.6%.[26]

• In 36 volunteers, intravenous azimilide 0.1 to 2.0 mg/kg over a 17- to 18-minute infusion period produced a dose-related increase in QT_c interval. Significant mean increases compared with baseline were observed in the 1.4 and 2.0 mg/kg dosage groups. At dosages of 0.8 to 2.0 mg/kg, a maximal decrease in HR of 22 beats/min was observed. No clinically significant alterations in PR and QRS intervals were noted.[26]

• Two small studies (n = 35 and n = 7) have investigated the effects of azimilide in patients with PES-induced, sustained ventricular tachycardia. Loading doses of azimilide were administered over a 4-day period, followed by once daily maintenance doses. In 4 of 21 patients, treatment with azimilide at dosages of 50 to 125 mg/day produced complete suppression with 3 extra stimuli in the right ventricular apex and outflow tract.[26]

2. Pharmacokinetic Profile

• The pharmacokinetic profile of azimilide is dose-proportional over the range 35 to 200mg[26] and is not influenced by age.[27,28] Absorption is complete after oral administration, and is unaffected by the presence of food.[26]

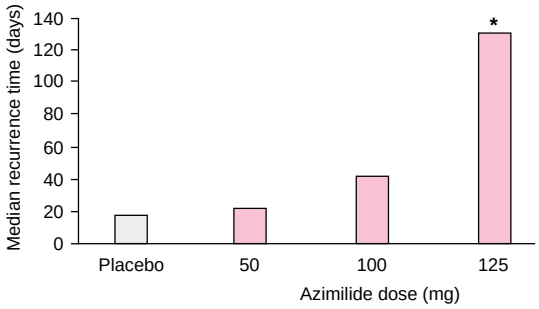

Fig. 2. Antifibrillatory efficacy of azimilide. Time to first symptomatic recurrence of atrial fibrillation or atrial flutter in 367 patients treated with oral azimilide 50, 100 or 125mg or placebo; * $p < 0.01$ *vs* placebo.[30]

• After a single oral dose of azimilide 150mg in male (n = 33) and female (n = 33) volunteers, peak blood concentrations (C_{max}) were achieved within 5.2 to 5.6 hours after administration. Mean C_{max} was significantly (p = 0.0001) higher in women than in men [207 *vs* 152 μg/L (0.39 *vs* 0.29 μmol/L)]. However, when adjusted for bodyweight, no gender difference was apparent. The areas under the blood concentration-time curves (AUC_∞) were similar in men and women. The apparent volume of distribution of azimilide in the terminal phase (V_z) was 26 L/kg and the drug was 94% bound to plasma protein. These parameters were unaffected by gender.[28]

• The terminal elimination half-life ($t_{½z}$) of azimilide was ≈4 to 5 days and the oral clearance (CL) was 0.15 L/h/kg.[28] Azimilide undergoes extensive hepatic metabolism,[29] and renal clearance (CL_R) accounts for <10% of total clearance (0.009 and 0.012 L/h/kg in men and women, respectively).[28] The only metabolite of azimilide that exhibits class III antiarrhythmic activity is found in the plasma at concentrations <5% of the parent drug.[26]

• In individuals receiving digoxin therapy (n = 18), azimilide at steady-state levels (after 5 days administration) produced a small elevation in the rate of absorption of digoxin and in its renal clearance. Changes were not clinically significant, and digoxin dose adjustment is not necessary during concomitant treatment with azimilide.[26]

• No pharmacokinetic interactions were noted during coadministration of azimilide and warfarin over 5 days in 34 individuals. Consequently, dosage adjustment is not required when azimilide is administered to patients receiving warfarin therapy.[26]

3. Therapeutic Trials

• A series of studies has evaluated the clinical efficacy of azimilide within the Azimilide Supraventricular Arrhythmia Program (ASAP), involving approximately 1000 patients with atrial flutter, atrial fibrillation or paroxysmal supraventricular tachycardia (PSVT).

• In one trial, a total of 367 patients with a documented history of atrial fibrillation, atrial flutter, or both (but in sinus rhythm at enrolment) were randomised to receive either placebo or azimilide 50, 100 or 125mg. Study treatments were administered orally as twice daily loading doses for the first 3 days, and once daily thereafter. The primary outcome measure was time to first symptomatic recurrence of atrial fibrillation/flutter. In patients treated with azimilide 125mg, the median recurrence time was significantly increased compared with that in placebo-treated patients (130 *vs* 17 days; p = 0.002) [fig. 2].[30]

• In another study, azimilide 125mg showed no benefit over placebo in patients with atrial fibrillation/flutter (n = 422) or PSVT (n = 60). The median times to arrhythmia recurrence in active and placebo groups, respectively, were 38 and 27 days (p = 0.29) in patients with atrial fibrillation/flutter,[31] and 180 versus 135 days (p = 0.55) in patients with PSVT.[32]

• In 3 randomised double-blind placebo-controlled studies involving a total of 133 patients with symptomatic PSVT, oral azimilide was administered (on an outpatient basis in >90% of patients) at dosages of 35, 75 or 100mg once daily (following a 3-day loading phase of twice daily administration) over a 180- to 270-day period. Azimilide

showed dose-dependent effects over the range tested. At a dose of 100mg, azimilide produced clinically significant treatment effects with a hazard ratio (placebo : azimilide) of 2.35 (CI 1.18 to 4.68; p = 0.015).[33]

• The efficacy of azimilide is currently being evaluated in recent (6 to 21 days) postmyocardial infarction patients at high risk of sudden cardiac death. The AzimiLide post-Infarct surVival Evaluation (ALIVE) is a randomised double-blind placebo-controlled multinational study investigating the potential for oral azimilide 100mg once daily to improve survival in a 1-year longitudinal study of patients most likely to benefit from antiarrhythmic therapy.[34]

4. Tolerability

• The safety of oral or intravenous azimilide has been evaluated in >500 volunteers who participated in phase I studies. Azimilide was generally well tolerated, and no arrhythmic events were reported after intravenous administration at doses up to 8 mg/kg. In a 14-day study of oral azimilide 35 to 200mg once daily, asymptomatic arrhythmias occurred in 7 of 84 (8%) and 3 of 35 (9%) patients receiving azimilide and placebo, respectively.[26]

• Tolerability data are available from more than 1000 patients with atrial fibrillation/flutter or PSVT who participated in placebo-controlled studies evaluating the efficacy of oral azimilide 35 to 125mg. Headache was the most commonly reported adverse event.[30] Azimilide 125mg was associated with a significantly ($p < 0.05$) lower incidence of fatigue (31 *vs* 44%) and dyspnoea (27 *vs* 42%) than placebo.[32]

• No arrhythmic episodes or serious adverse events were reported in 37 patients with atrial fibrillation or atrial flutter who received intravenous azimilide (4 or 8 mg/kg).[26] In clinical studies of oral azimilide 35 to 125mg in 906 patients with a history of atrial fibrillation/flutter or PSVT, torsades de pointes occurred in 5 patients receiving azimilide and in no patients on placebo. Torsades de pointes did not occur in any patients with PSVT.[33,35]

• Pooled data from 3 studies in patients with atrial fibrillation/flutter or PSVT indicate a hazard ratio (azimilide : placebo) for mortality of 0.77 (95% CI 0.19 to 3.1) and observed mortality rates of 3.0 and 4.0 per 100 patient-years in azimilide and placebo groups, respectively.[36]

• Open-label 3-year tolerability studies in more than 900 patients who completed the randomised phase of ASAP are ongoing. To date, the incidence of torsades de pointes and withdrawal due to serious adverse events has been low.[26]

5. Azimilide: Current Status

Azimilide is a class III antiarrhythmic agent that blocks I_{Ks} and I_{Kr}, and appears to be rate-independent *in vivo*. The drug is in late phase clinical trials for the treatment of atrial fibrillation, atrial flutter and PSVT. Further studies are being planned to demonstrate the unequivocable efficacy of azimilide for these indications. The efficacy of azimilide is also being evaluated in a multinational clinical trial in recent postmyocardial infarction patients at high risk of arrhythmia-induced sudden cardiac death.

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