Effects of Intravenous Amiodarone and Ibutilide on Action Potential Duration and Atrial Conduction Kinetics in Patients With Persistent Atrial Fibrillation

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SUMMARY

Class III antiarrhythmic drugs have been shown to be effective for termination of atrial fibrillation (AF). The aim of this study was to determine the steady state and non-steady state effects of amiodarone and ibutilide on the atrial monophasic action potential (MAP) duration (MAPD), effective refractory period (ERP), and intra-atrial conduction time (IACT) in human persistent AF.

Fourteen patients with persistent AF who underwent internal atrial defibrillation were included in the study. The atrial MAP was recorded at the high right atrium. IACT was measured from the pacing spike to the distal coronary sinus. MAPD and IACT were assessed during the steady state and at the shortest diastolic interval (DI) at a basic cycle length (CL) of 600 msec and after a premature stimulus. Amiodarone did not affect MAPD or the ERP at the basic CL, but it increased MAPD at the shortest DI. Amiodarone increased IACT at both the basic CL and the shortest DI. Ibutilide increased the MAPD and ERP at the basic CL and at the shortest DI. Ibutilide did not affect IACT at the basic CL or the shortest DI.

Ibutilide increases atrial MAPD not only in the steady state but also at the shortest DI, but it does not affect IACT in patients with persistent AF. Amiodarone does not affect MAPD or ERP, but it increases IACT in the steady state, and it increases MAPD and IACT at the shortest DI. (Int Heart J 2014; 55: 244-248)

Key words: Internal atrial cardioversion, Electrical remodeling, Monophasic action potential, Class III antiarrhythmic drug

Atrial fibrillation (AF), the most common sustained arrhythmia encountered in clinical practice, can result in a wide range of complications,¹⁾ and its treatment remains problematic.²⁾ A better understanding of the mechanisms determining antiarrhythmic drug efficacy would help to improve therapy. Under awareness of the risks of potent class I antiarrhythmic drugs made apparent by the Cardiac Arrhythmia Suppression Trial and subsequent analysis, developers shifted to class III antiarrhythmic agents.²⁻⁴⁾ Clinical trials have shown class III drugs to be relatively ineffective in terminating AF but effective in preventing its recurrence.⁵⁾ Experimental studies in vagotonic and atrial tachycardia-related models of sustained AF have shown limited ability of clinically-relevant doses of class III rapid delayed rectifier (I_{Kr})-selective blocking agents to terminate AF.⁶⁻⁸⁾ Wang, *et al* showed that reverse use-dependent actions may limit class III drug efficacy at the rapid rates of AF but permit such drugs to prevent AF induction by premature complexes at slower resting sinus rates.⁶⁾ Recent experimental studies have shown that persistent AF causes progressive electrophysiologic changes in the atrial myocardium

that make the atria more vulnerable to fibrillation.^{9,10)} Furthermore, study of atrial action potential duration restitution (APDR) kinetics in human AF has revealed that AF is related to steeply sloped (> 1) APDR kinetics.¹¹⁾ Thus, it is plausible to assume that this process of electrical remodeling during persistent AF also influences the efficacy of antiarrhythmic drugs.

We have reported that rate-dependent steady-state electrophysiologic effects of class III antiarrhythmic drugs nifekalant, amiodarone, and ibutilide on the atrium differ in patients with persistent AF.¹²⁾ However, the effects of class III antiarrhythmic drugs on the non-steady-state atrial action potential duration remain unclear. We therefore designed the present study to investigate the steady-state and non-steady-state electrophysiologic effects of two different class III agents, amiodarone and ibutilide, on the remodeled atrium in patients with persistent AF.

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METHODS

Patients: Subjects of the study were 14 patients (11 men, 3 women; mean age 55.7 ± 14.2 years, range 34-73 years) with non-valvular chronic AF lasting more than 2 months (13.7 ± 17.3 months, range 2-66 months) and referred to Nihon University Hospital for cardioversion of the persistent AF between December 1999 and July 2004. External cardioversion had failed in these patients, so they agreed to undergo internal atrial cardioversion. Exclusion criteria for the study were a corrected QT interval of > 440 ms and left ventricular ejection fraction of $< 45\%$. All patients provided written informed consent for participation in this study, which involved internal atrial defibrillation, electrophysiologic study, and intravenous administration of amiodarone or ibutilide. The study was approved by the Clinical Research Committee of Nihon University Hospital.

Internal cardioversion: Internal cardioversion was performed via two 6F decapolar electrodes (electrode length: 5 mm; interelectrode distance: 2 mm; ELECATH, Electro-Catheter Corp., Rahway, NJ, USA) positioned in the right atrial appendage and distal coronary sinus. Biphasic shocks of 3 ms/3 ms were used for cardioversion of the AF (HVS-02; Ventritex, Sunnyvale, CA, USA). Biphasic shocks were started at 100 V/100 V and increased by increments of 50 V until cardioversion occurred. Cardioversion at a mean energy of 8.7 ± 3.9 J was successful and without complications in all 14 patients.

Study protocol: Treatment with antiarrhythmic drugs (excluding digitalis, beta blocker, and calcium channel antagonist) was discontinued at least 5 half-lives before the electrophysiologic procedure. No patient already treated with amiodarone was included in the study. Amiodarone (Taisho Pharmaceuticals, Inc., Tokyo) was administered intravenously at a dose of 5.0 mg/kg to 8 patients, and ibutilide (Pharmacia & Upjohn Company, Kalamazoo, MI, USA) was administered at a dose of 0.01 mg/kg to 6 patients. These amounts were based on average clinical doses, and each drug was administered 10 minutes after successful cardioversion. A decapolar electrode catheter (electrode length: 1 mm, interelectrode distance: 2.5-2 mm, St. Jude Medical, Minneapolis, MN, USA) was placed in the coronary sinus, and a Franz combination catheter (EPT Ltd., Sunnyvale, CA, USA) was placed in the high right atrium. Recordings were obtained before administration of the drug and then 15 minutes after bolus administration of amiodarone in the amiodarone group and 5 minutes after bolus administration of ibutilide in the ibutilide group. Atrial pacing was performed from the proximal bipolar electrodes of the Franz catheter. Monophasic action potential duration (MAPD) was recorded by pressing the Franz catheter against the atrial wall. The right atrium (RA) was paced at a cycle length (CL) of 600 ms for 12 beats (S1) at an output of twice the late diastolic threshold and

pulse duration of 2 ms, and an extrastimulus (S2) was delivered in 20-ms decrements until a coupling interval (CI) of 400 ms was reached, in 10-ms decrements until a CI of 300 msec was reached, and at 5-ms decrements until the effective refractory period (ERP) was reached. When MAPs appeared unstable or small during pacing, we pushed the Franz catheter against the RA wall at a location within 10 mm of the previous position until stable MAPs were once again recorded. Right atrial MAPs were recorded during atrial pacing at a filter setting of 0.05-500 Hz. MAPD at 90% repolarization was measured. The diastolic interval (DI) was measured from the time of MAPD at 90% repolarization of the last S1 to the steepest upstroke of the MAP of S2. Intra-atrial conduction time (IACT) was measured from the start of the pacing spike recorded on the atrial electrogram by the distal pair of electrodes of the decapolar catheter placed in the coronary sinus.

Statistical analysis: Values are expressed as the mean $\pm$ SD. The clinical characteristics of the patients were analyzed using the Mann-Whitney *U* test. Differences between pre- and post-treatment MAPD, ERP, and IACT within each group were analyzed by the Wilcoxon signed-rank test. A *P* value of < 0.05 was considered statistically significant. All statistical analyses were performed with Stat View 5.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Clinical characteristics of the study patients: There were no significant between-group differences in age, sex ratio, AF duration, left atrial diameter, left ventricular ejection fraction, internal atrial cardioversion energy, or plasma brain natriuretic peptide level (Table I).

RA MAPD: The effects of amiodarone and ibutilide on RA MAPD in the steady state and at the shortest CI are shown in Figures 1 and 2 and Table II. RA MAPD did not change significantly with amiodarone at the steady-state CL, but with ibutilide, RA MAPD increased significantly at the steady-state CL, from 189.3 ± 19.8 ms to 220.7 ± 18.1 ms ($P = 0.028$) (Table II). The shortest DI increased significantly with amiodarone from 46.1 ± 18.5 ms to 63.0 ± 23.2 ms ($P = 0.012$), but it did not change significantly with ibutilide (Table II). MAPD at the shortest CI increased significantly with amiodarone from 132.4 ± 10.5 to 142.8 ± 16.8 ms ($P = 0.016$) and with ibutilide from 121.7 ± 17.6 to 144.5 ± 13.9 ms ($P = 0.043$) (Table II).

RA ERP: The late diastolic threshold ranged from 0.5 V to 1.5 V before drug administration and did not change with administration of amiodarone or ibutilide. The effects of amiodarone and ibutilide on the RA ERP are shown in Table II. The RA ERP did not change with amiodarone, but it increased significantly with ibutilide from 172.5 ± 19.9 ms to 215.0 ± 27.6 ms

Table I. Clinical Characteristics of the Study Patients ($n = 14$)

	Age (years)	Sex (M/F)	AF duration (months)	LA diameter (mm)	LVEF (%)	IACV energy (J)	Plasma BNP (pg/mL)
Amiodarone	59.5 ± 12.7	6/2	10.9 ± 9.1	43.2 ± 9.6	59.2 ± 12.6	8.9 ± 3.5	171.7 ± 112.7
Ibutilide	50.7 ± 15.6	5/1	18.5 ± 24.7	44.9 ± 5.6	64.2 ± 11.1	8.4 ± 4.7	90.9 ± 18.5
<i>P</i>	0.301	0.615	0.794	0.156	0.519	0.699	0.198

AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; IACV, internal atrial cardioversion; and BNP, brain natriuretic peptide. *P* were obtained using the Mann-Whitney *U* test.

Figure 1. Steady-state and non-steady-state effects of amiodarone on right atrial monophasic action potentials and intra-atrial conduction time before (A) and after (B) administration of amiodarone. RA MAP indicates right atrial monophasic action potential; RA MAPD, right atrial monophasic action potential duration; CS 1-2, bipolar electrogram from the distal pair electrodes in the coronary sinus; STIM, stimulation artifact; DI, diastolic interval; and IACT, intra-atrial conduction time.

Figure 2. Steady-state and non-steady-state effects of ibutilide on right atrial monophasic action potentials and intra-atrial conduction time before (A) and after (B) administration of amiodarone. RA MAP indicates right atrial monophasic action potential; RA MAPD, right atrial monophasic action potential duration; CS 1-2, bipolar electrogram from the distal pair electrodes in the coronary sinus; STIM, stimulation artifact; DI, diastolic interval; and IACT, intra-atrial conduction time.

Table II. Effects of Amiodarone and Ibutilide on Steady-State and Non-Steady-State Atrial Electrophysiologic Variables						
	Steady state (CL: 600 ms)			Non-steady state (shortest CI)		
	MAPD	ERP	IACT	Shortest DI	MAPD	IACT
Amiodarone						
Before	200.8 ± 16.4	214.3 ± 25.6	130.1 ± 25.3	46.1 ± 18.5	132.4 ± 10.5	168.3 ± 30.1
After	201.8 ± 20.5	210.0 ± 31.2	136.3 ± 28.4	63.0 ± 23.2	142.8 ± 16.8	196.6 ± 36.0
P	0.735	0.751	0.017	0.012	0.016	0.018
Ibutilide						
Before	189.3 ± 19.8	172.5 ± 19.9	144.0 ± 14.7	0.5 ± 14.4	121.7 ± 17.6	206.5 ± 24.5
After	220.7 ± 18.1	215.0 ± 27.6	141.3 ± 15.0	11.8 ± 33.8	144.5 ± 13.9	216.2 ± 39.4
P	0.028	0.028	0.492	0.463	0.043	0.345

Before and after values are shown in milliseconds. *P* were obtained using the Wilcoxon signed-rank test. CL indicates cycle length; CI, coupling interval; MAPD, monophasic action potential duration; ERP, effective refractory period; IACT, intra-atrial conduction time; and DI, diastolic interval.

($P = 0.028$) (Table II).

IACT: The effects of amiodarone and ibutilide on steady-state IACT and IACT at the shortest DI are shown in Table I. IACT increased significantly with amiodarone administration at the steady-state CL, from 130.1 ± 25.3 ms to 136 ± 28.4 ($P = 0.017$), and IACT was further increased at the shortest DI from 168.3 ± 30.1 to 196.6 ± 36.0 ms ($P = 0.018$) (Table II). IACT did not change significantly with ibutilide in the steady state or at the shortest DI (Table II).

DISCUSSION

Major findings: In the present study, we evaluated the electrophysiologic effects of the class III antiarrhythmic drugs amiodarone and ibutilide on the atrium in patients with persistent AF. Intravenous administration of ibutilide increased the steady-state RA MAPD and the ERP, and the effect of ibutilide on RA MAPD at the shortest CI was maintained, although the increase was smaller than in the steady state. In contrast, intravenous administration of amiodarone did not affect steady-state RA MAPD or the ERP, but it significantly increased RA MAPD at the shortest DI. Ibutilide did not affect IACT in the steady state or at the shortest CI. Amiodarone increased IACT in the steady state and further increased IACT at the shortest DI. Ibutilide did not affect the shortest DI significantly; amiodarone, however, increased the shortest DI significantly.

Effects of class III antiarrhythmic drugs in the remodeled human atrium: Experimental and clinical studies have established that AF induces a shortening of atrial refractoriness (electrical remodeling).^{10,13-15} This AF-induced shortening of atrial action potential is due to downregulation of a number of ionic currents (electrical remodeling). The L-type Ca^{2+} (I_{CaL}) current, the transient outward current (I_{to}), and the ultrarapid delayed rectifier current (I_{Kur}) are reduced after prolonged rapid atrial pacing or AF.¹⁶⁻¹⁸ However, differences in rate-dependent changes in atrial MAPD exist between rapid pacing-induced AF in animals and AF in humans. van der Velden, *et al* showed that AF-induced electrical remodeling in goats comprises shortening of the atrial MAPD and reversal of the physiologic adaptation of atrial ERP to heart rate.¹⁸ However, atrial MAPD and ERP in patients with persistent AF show rate-dependent shortening.^{13-15,19} Furthermore, Kim, *et al* showed persistent AF to be related to steeply sloped (> 1) APDR, which results in shorter RA MAPD following the shortest DI.¹² Amiodarone blocks multiple channel currents (I_{Na} , I_{CaL} , I_{to} , I_{Kr} , and I_{Ks}).²⁰ However, the short- and long-term effects of amiodarone have been shown to differ, i.e., the main short-term effect of amiodarone is inactivation of the ion channel currents I_{Na} , I_{Ca} , and I_{Kr} , and $I_{\text{K}_{\text{Ach}}}$.^{21,22} In the present study, amiodarone did not affect the steady-state RA MAPD or ERP, but it increased RA MAPD at the shortest DI. It is possible that the increased RA MAPD at the shortest DI is due to the I_{Na} channel blocking effect of amiodarone. Amiodarone increased the steady-state IACT and further increased the IACT at the shortest DI. Another study from our laboratory showed that intravenous administration of amiodarone in patients without AF significantly increases RA MAPD and ERP to a similar extent at pacing CLs of 600 and 350 ms.²² IACT was slightly increased at pacing CLs of 600 and 350 ms, but the increase did not reach statistical significance.²² Therefore, the effects of intravenous

amiodarone might be influenced by atrial electrical remodeling of the inactivated I_{Na} channel.

Intravenous administration of ibutilide has been reported to terminate AF in 31% of patients.²³ With respect to its mechanism of action, ibutilide has been shown to activate the slow inward Na^{+} current²⁴ and to block the rapidly activating delayed rectifier K^{+} current.²⁵ Our laboratory has shown that intravenous administration of ibutilide in patients without AF significantly increases RA MAPD and the ERP at pacing CLs of 600 ms and 350 ms in a weak reverse rate-dependent manner and that IACT does not change at pacing CLs of 600 ms and 350 ms.²⁶ In the present study also, ibutilide increased the steady-state RA MAPD, ERP, and RA MAPD at the shortest DI. In contrast, ibutilide did not affect the IACT in the steady state or at the shortest DI. Therefore, the electrophysiologic effects of intravenously administered amiodarone on the remodeled human atrium might occur mainly through the Na^{+} channel-blocking effect, whereas the electrophysiologic effects of intravenously administered ibutilide might occur mainly through the delayed rectifier K^{+} current.

Clinical implications: The current study revealed that ibutilide administration resulted in an increase in RA MAPD at the steady state and at the shortest coupling interval without affecting IACT. These effects may explain the relatively high rate of AF termination by ibutilide. The present study also showed that intravenous administration of amiodarone did not affect the atrial MAPD and ERP but increased IACT at steady state, but increased RA MAPD to a lesser extent compared to amiodarone and further increased IACT at the shortest coupling interval. Therefore, intravenous administration of amiodarone may also be useful for termination of AF in patients with electrically and structurally remodeled atria.

Study limitations: Our study was limited by the small study groups, the wide variation in the duration of AF between individual patients, and the fact that only one drug dose was tested in each group. We did not compare the effects of each drug between patients with and without AF, nor did we calculate maximum slope from the APDR curve because of MAP amplitude diminution during the baseline and post-drug administration studies.

Conclusions: Our study results lead us to conclude that ibutilide increases the atrial action potential duration and ERP in the steady state and at the shortest DI and that it does not affect the intra-atrial conduction time in the steady state or at the shortest DI. Intravenous amiodarone does not affect steady-state atrial action potential duration or the ERP, but it does increase atrial action potential duration at the shortest DI and increase intra-atrial conduction time in the steady state and at the shortest DI. Our findings suggest that the efficacies of these class III antiarrhythmic drugs are brought about by different electrophysiologic mechanisms in patients with persistent AF. Further clinical investigation is needed to confirm these findings.

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